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VENOUS THROMBOSIS, PULMONARY INFARCTION AND EMBOLISM FOLLOWING GYNÆCOLOGICAL OPERATIONS

By H. H. Hampton and Lawrence R. Wharton

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Introduction

Since Virchow's monumental work, thrombosis and embolism have held the attention of pathologist, internist and surgeon, and, as a result, a vast amount of literature has accumulated. Our personal interest was aroused recently by several consecutive deaths from pulmonary embolism, constituting 50 per cent of our fatalities for the past year. It was quite evident from the onset that prevention of embolism in our clinic, if attainable in any degree, would depend upon an accurate study of our cases of phlebitis and thrombosis. We have therefore collected statistics embracing all the cases of phlebitis and thrombosis that have occurred since the opening of our clinic in 1889. About 40 of these cases have been previously reported in excellent papers by John G. Clark [1] and by Benjamin R. Schenck.[2]

We had been engaged in compiling our statistics but a short while when we made the observation that, in the case of many patients with phlebitis who later developed pulmonary complications, a diagnosis of pleurisy or pneumonia had been made without any reference to the possibility of infarction. We noticed, moreover, that a certain number of our patients who had suffered from an unrecognized pulmonary infarction died later of pulmonary embolism.

The second half of our paper, therefore, we shall devote to the pulmonary complications associated with venous thrombosis. In doing this we shall attempt to show that these conditions have often been overlooked and shall present the clinical data on the basis of which we think they may be recognized. We are presenting these subjects entirely from a clinical viewpoint, having conducted no experiments upon either thrombus formation or infarction. We have made rather free use of the literature, however, and in practically all of our fatalities fortunately have been able to check our clinical findings by post-mortem examinations.

Post-Operative Venous Thrombosis

The Pathology of Thrombosis

Among pathologists, Dr. William H. Welch [3] stands out pre-eminently for his broad vision of the whole subject. In

preparing this paper, we have liberally used his article, which is to be found in "Allbutt's System of Medicine."

What are the factors concerned in the production of thrombosis? Following the classification of previous observers we might conveniently bring them under two heads—*primary* and *contributory*. Under *primary* we would place infection and trauma, and under *contributory*, slowing of the blood stream, chemical and physical changes in the blood and anatomical relations of the blood-vessels.

We can no more attribute all cases of thrombosis to a single cause than we can the failure of a corn crop. The crop failure may be due to drought, lack of fertility, parasites, poor cultivation, or to all these conditions working together. So with venous thrombosis; there is practically always more than one single etiological factor to be considered. In a case of phlegmasia alba dolens very few will deny that infection plays the major rôle. In the occurrence of thrombosis following a clean abdominal operation, however, it is rather hard to draw an indictment against infection.

The process of thrombus formation has been studied extensively by many pathologists. It is practically agreed that the thrombus is first represented by a collection of blood-platelets; in a few minutes leucocytes and fibrin are added to the picture. The thrombus may be described as leucocytic or fibrinous, depending upon which of these two elements dominates. Of this much we are fairly certain; but when we make inquiry as to what induces the endothelial injury that causes the collection of platelets and leucocytes, we are broaching a question that is still open. Is it the presence of traumatism, toxins or actual bacterial invasion? All these questions must be answered upon sound experimental evidence before we arrive at a clear understanding of thrombus formation.

Even without this knowledge, however, on the basis of clinical observation we have a certain right to speculate as to the principal causes of this condition. We do know that patients come to us in the pink of condition, have clean laparotomies and yet develop thrombosis of the leg veins. We are naturally justified in assuming, therefore, that operation has furnished all the necessary conditions for the development of thrombosis. This complication is not peculiar to any single type of operation, although it is most common after a laparotomy. What factors conducive to thrombosis, then, are common to all operations? Traumatism of the tissues is certainly one; furthermore, we believe it is generally agreed that there is no such thing as an operation without the introduction of organisms.

The important part that operative procedures play in the production of thrombosis is readily seen by a glance at that group of cases in which thrombosis is most often found—myomata of the uterus. We are reporting 69 cases of myoma in which thrombosis developed after operation. Of these patients, 17 per cent were anæmic, 24 per cent were suffering from infections in the fallopian tubes, and a large number had pelvic congestion with dilated veins and lymphatics. These are the conditions that are supposed to favor thrombus formation. Yet only one patient out of the 69 had developed thrombosis prior to the operation. This seems to indicate that the operation furnished the conditions necessary to thrombus formation.

What is there peculiar to a hysterectomy for myoma that contributes to thrombosis? The abdomen is usually opened through a long midline incision. The tumor is delivered by sharp dissection through an area almost free from blood-vessels. The edges of the wound in the abdominal well are protected from infection by wet gauze. In all hysterectomies we clamp large vessels, sutures at times break and are replaced. It is sometimes difficult to be sure that vessels are not traumatized proximal to the point of ligature. A certain number of myomata extend into the broad ligaments and when enucleated leave behind a large raw bed of traumatized tissue. The vaginal vault, moreover, is richly supplied with large venous plexuses, which in multiparæ are often tortuous and varicose. In low cervical amputations and in all panhysterectomies, these vessels must be cut and ligated. During the release of the bladder from its uterine attachments, another large vascular area is handled. All these procedures involve trauma and the possibility of subsequent thrombosis.

Infection, also, has an open door here. In hysterectomies the cervical canal or vaginal vault is always opened. The fallopian tubes, moreover, often harbor old chronic inflammatory processes. In all probability the cervical canal, the vaginal vault and the fallopian tubes form the usual portals of entry for organisms. It does not seem unreasonable to suppose that here should be a potential source of infection, when to the normal flora we have added the possibility of secondary contamination in the presence of traumatized tissue.

Here, then, we have a fertile field for the development of thrombosis—traumatized tissue and blood-vessels in the presence of organisms. It seems, therefore, that infection and trauma to the pelvic vessels are concerned in the great majority of cases of post-operative thrombosis. We cannot agree with Clark that most cases of femoral thrombosis develop from the inferior or deep epigastrics; nor does the evidence obtained from the autopsy table seem to support this contention. It may be, however, that some thromboses following the Gilliam suspension of the uterus have their origin in the manner that Clark has described.

Why is thrombosis more common in the left than in the right leg? The anatomical differences in the return circulation of the two sides are always cited by way of explanation, but the many unsuccessful attempts to answer this question merely serve to remind us that we do not yet understand all the conditions favoring venous thrombosis.

Prophylaxis.—We hoped to plot a curve that would show a decrease of thrombosis as the technique of the operating room improved. This was so irregular, however, that nothing could be derived from it. During the last three years there has been a marked decrease in the number of these cases.

It seems that our only hope for reducing the frequency of this complication lay in the constant care of details during the operation, the gentle handling of tissues and the use of sharp dissection wherever possible. Examination of the legs for thrombosed or varicosed vessels should always be made before operation. The legs should not be bound too tightly with straps. We cannot see any harm from the use of the Trendelenburg posture wherever necessary. In laparotomies care should be exercised in using deep or heavy retractors. In spite of the fact that we have used this precaution systematically, the examination of the peritonæum over the region of the iliac vessels not infrequently has shown evidence of traumatism. We agree with the Mayos[4] in getting our patients out of bed early. In letting up a patient that has an unexplained temperature, however, we feel that one should proceed cautiously.

The Clinical Aspects of Thrombosis.—The cases of thrombosis which we present occurred after operations performed between the years 1890 and 1918 inclusive. During this period of almost 30 years, about 21,000 patients were operated upon in the gynæcological clinic. In this number are included all types of operations, both perineal and abdominal. During this period there have been 205 cases of femoral thrombophlebitis; in other words, the incidence of thrombosis following all types of gynæcological operations is about 1 per cent. This agrees closely with the results in other clinics. Klein,[5] of Vienna, reported, in 1911, 70 cases of thrombosis following 5851 operations, a frequency of 1.2 per cent. Franz[6] found an incidence of 1.8 per cent. Bondy[7] in 1000 gynæcological operations and Ranzi[8] in 6871 cases reported 1.3 per cent and 1.2 per cent respectively.

In an almost overwhelming majority of our cases thrombophlebitis occurred after a laparotomy. Of our 205 cases of thrombosis, 81 per cent followed abdominal operations, 31 per cent supravaginal hysterectomy, 11 per cent panhysterectomy, 16 per cent operations on the adnexa, 10 per cent suspensions of the uterus, 5 per cent myomectomy, 8 per cent some perineal operation. Klein reports that 56 per cent of his 70 cases occurred after laparotomy.

Of our 205 patients, 69 were operated upon for myomata of the uterus. This constitutes by far the largest single group. In association with post-operative thrombosis, 34 per cent of our series of thrombosis followed myoma operations—in 8 per cent the myomata were complicated by salpingitis and were primarily infected cases. Next in importance to myomata comes the group of salpingitis, pyosalpinx and similar infections of the fallopian tubes. Fourteen per cent of our cases of thrombosis followed some operation done to relieve this condition. Ovarian cysts almost equal the group of inflammatory conditions in the incidence of thrombosis, for 13 per cent of our thromboses were associated with the removal of cystic tumors of the ovary. Six per cent followed panhysterectomy for carcinoma of the cervix; 1 per cent carcinoma of the fundus; 7 per cent suspension of the uterus; 8 per cent perineal operations, and 4 per cent appendectomies. The remaining cases of thrombosis were divided in an almost equal ratio among operations on the kidneys, gall-bladder, extra-uterine pregnancy, vesico-vaginal fistula and rectal operations.

From this comparison it is clearly evident that venous thrombosis and the removal of large pelvic tumors, particularly myomata and ovarian cysts, are closely associated. This has been a matter of common observation among gynæcologists for some time. According to statistics on this subject, it is practically certain that in 100 hysteromyomectomies from three to five of the patients will develop the clinical signs and symptoms of thrombophlebitis of the leg. Kelly and Cullen[9] noted that thrombosis followed hysterectomy for myoma in 3 per cent of their cases; Klein reported 3.3 per cent in 730 myoma operations; Zurhelle,[10] 2.7 per cent; Bruckhard,[11] 4.6 per cent in 236 operations. The endeavor to explain the heavy incidence of thrombosis following myoma operations has evoked many speculations. These are discussed in another part of this paper.

Strassmann and Lehmann[12] laid great stress on changes in the cardiac musculature in myomata. They claimed that in 40.8 per cent of all cases of myomata they were able to find a cardiac lesion, and called this syndrome the "myoma heart." Klein seems to support this view. Unfortunately, we cannot see that there is any such direct connection between the cardiac musculature and myomata of the uterus. Although we have seen many patients suffering with myomata who also showed pronounced symptoms referable to cardiac insufficiency, our experience would indicate that these symptoms are almost always due to concomitant factors which of themselves would increase the load of the heart, such as prolonged secondary anæmia due to persistent uterine bleeding over a long period of time, the venous congestion incident to a large intra-abdominal mass, the additional body weight of a parasitic tumor and the poor general condition of some of these patients. These factors, we believe, are sufficient to account for most of the cardiac symptoms seen in myoma cases.

Furthermore, in 19 autopsies performed on patients dead of pulmonary embolism following venous thrombosis after pelvic operations, 10 of which were hysterectomies, there were no cardiac charges which could support the view of Strassmann and Lehmann. In several of these cases, moreover, the myomata were as large as one usually finds. Kelly and Cullen have investigated this subject in an exhaustive manner and have expressed their views in the large volume on "Myomata of the Uterus," published in 1906. Their conclusions and ours are essentially the same, both arrived at independently.

The Vessels Involved in Thrombosis.—In almost all writings on this subject, the frequency of thrombosis of the veins of the left leg has been emphasized. This fact is very evident in the present group of cases, where in 66 per cent the vessels of the left leg were involved, in 24 per cent of the right and in 9 per cent of both legs. In one instance the vessels involved were in the left arm, in another the superficial veins of the neck and in a third the mesenteric veins.

In the left leg the vessel usually involved was the femoral vein (40 per cent), the left saphenous in 12 per cent and the left popliteal in 2 per cent. In the right leg the femoral vein was involved in 10 per cent of the cases and the saphenous in 7 per cent.

In all of these instances the thrombosis was clinically evident from characteristic signs and symptoms. At the autopsy table, however, in patients dead of pulmonary embolism, thrombosis is discovered in places, rendering the diagnosis much more difficult, as, for example, in the veins of the pelvis. As a result of our study of the clinical picture of thrombophlebitis, we have been led to believe that many cases of unexplained post-operative elevation of temperature, particularly those occurring during the second and third weeks of convalescence, may be due to phlebitis and thrombosis of some of these venous trunks which are so situated as not to cause a clean-cut clinical picture and which are usually recognized only on the autopsy table casually or in the search for the source of a fatal pulmonary embolus.

With the view of determining, if possible, any factors predisposing to phlebitis or thrombosis, we have studied our cases from various aspects—the pre-operative condition, the type of operation done, the indication for drainage, the relation of previous pregnancy, the age of the patients and the time of operation. The pre-operative condition of these patients on the whole was satisfactory. Two-thirds of them were in good condition, were well nourished and without any elevation of temperature; 13 per cent were in fair condition; 15 per cent were anæmic, with a hæmoglobin of less than 65 per cent, while only 8 per cent were clearly poor surgical risks. Of all these patients only 28 per cent had a temperature of 99° or higher on admission. Eighty-one per cent were married; 19 per cent single; 73 per cent parous; 27 per cent nulliparous, the sterility being due usually to myomata or salpingitis. Seventy-seven per cent were "clean" cases, 23 per cent were infected cases from the beginning; 33 per cent were drained at operation and 67 per cent were not. The ages were equally divided between 20 and 50, with a very few cases beyond each limit. Whether there is any association between any of these data and thrombosis remains doubtful.

The Clinical Picture of Thrombosis.—The clinical picture of thrombosis is too well known to require or merit much attention. Matters of common knowledge will be merely mentioned. There are one or two points, however, which, according to the literature, seem rather confused, and with regard to these we shall give our results in greater detail.

The first item of interest in our cases of thrombophlebitis is that practically none of the patients showed an absolutely normal convalescence up to the onset of the clinical manifestations of thrombosis. The one point of variance from the normal was in the temperature curve.

In the usual post-operative convalescence in a clean case, we expect the temperature to reach normal and remain there by the end of the first week, or certainly during the second week. In our cases of thrombosis, this is not the rule; in fact, it is clearly the exception. Almost without exception our patients have shown a definite, low, persisting pyrexia from shortly after the time of operation until the onset of pain and swelling of the leg, during a period when the temperature should clearly be normal. This temperature is usually not high; its most frequent variation is from 99° to 100°F. With this low fever the pulse usually remains low, the pulse curve either accompanying or falling below the temperature curve.

Michaelis[13, 14] has been one of the few and also one of the earliest observers to call attention to this point. He goes so far as to state that in patients who have a perfectly normal temperature curve after operation, thrombosis and embolism do not need to be feared. Michaelis has been contradicted by Küster,[15] who failed to notice this premonitory rise of temperature. G. Petrén[16] came to the conclusion in 1913 that in a majority of his cases this low febrile course was noted without other symptoms and like Michaelis believes it is of some value in warning one of the possible presence of an obscure thrombophlebitis. Mahler[17] stated that there was a premonitory rise in pulse before the thrombosis became evident, but that the temperature remained absolutely normal.

Some of these observers doubtless have been dealing with groups containing both post-operative and puerperal thrombosis, so that those which we are considering here may not be precisely similar. As regards post-operative thrombosis, however, on the basis of our findings in 205 cases, we believe we can affirm that the large majority of the patients have a persistent, low, unexplained elevation of temperature before the clinical evidence of the thrombosis becomes apparent. In such cases we believe the possibility of obscure thrombosis and subsequent infarction or embolism should always be kept in mind.

Signs and Symptoms of Thrombosis.—The symptoms of peripheral thrombosis are usually unmistakable. Pain is almost always the first complaint of the patient, and is usually the first symptom explanatory of the low fever. In rare cases, tenderness may be present along the course of the femoral vein before the onset of pain. The pain is sometimes very acute, requiring morphin, and is usually rather persistent, according to the severity of the thrombosis.

Swelling usually follows promptly and may be marked. It is limited to the region supplied by the vein thrombosed; in saphenous thrombosis, to the ankle and lower part of the leg; in popliteal, to the whole lower leg; in femoral, to the leg and thigh. Elevation of the surface temperature is common. Redness over the course of the vein is rather unusual; the limb occasionally becomes cyanotic.

It is well to remember, however, as Welch has pointed out, that thrombosis of a large vessel may be present with almost no swelling. This finding we have verified at autopsy both in regard to the femoral and saphenous veins, and on this basis can state that thrombosis of a large peripheral vein may be present without any local signs or symptoms whatever.

The temperature does not rise decidedly until the initial symptom of pain has become evident; in fact, there is usually

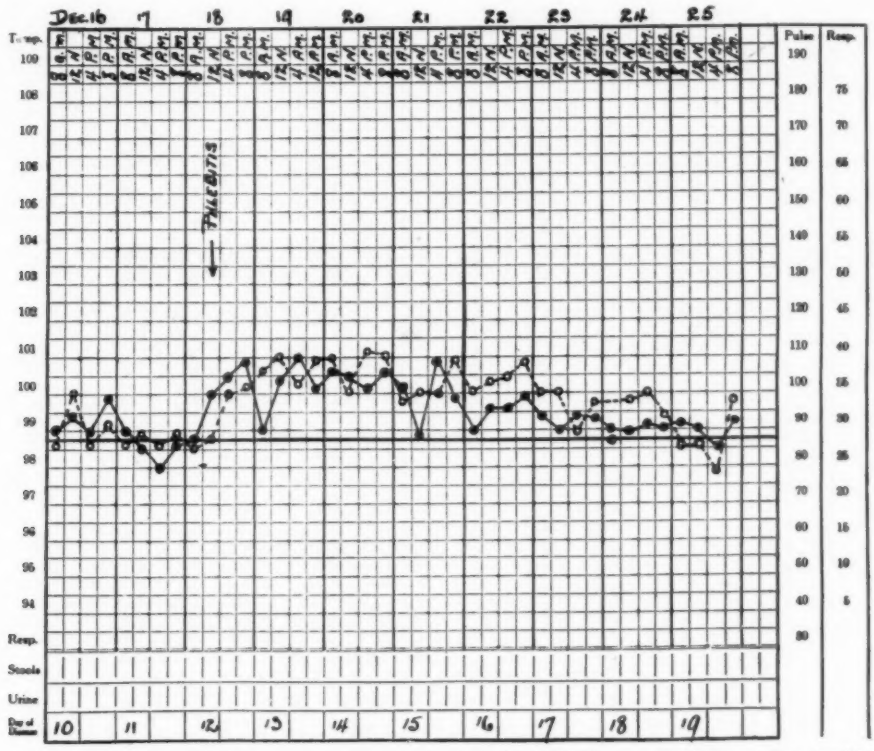

FIG. 1.—Temperature curve. Femoral thrombo-phlebitis, appearing on the twelfth day after operation. Gynæcological No. 20792. The dots and solid lines indicate the temperature; rings and dashes indicate the pulse.

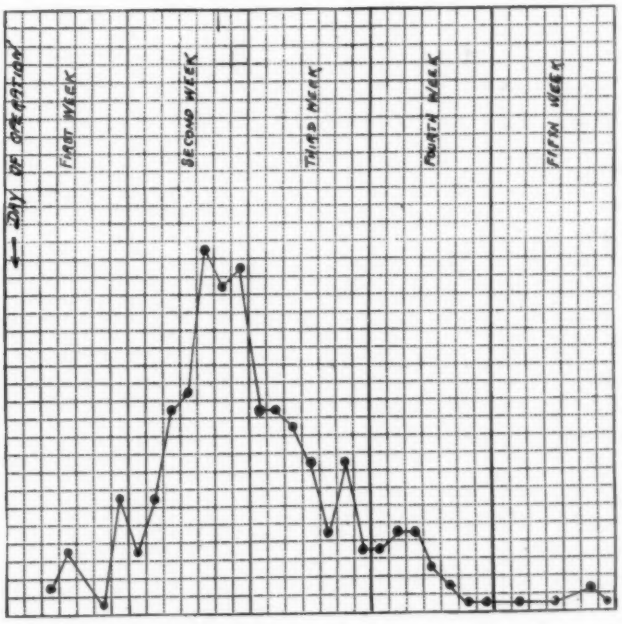

FIG. 2.—Curve of incidence of post-operative femoral thrombo-phlebitis, based on a series of two hundred and five cases.

no marked rise until 24 hours after the onset of pain. It may or may not precede the swelling. There is usually no marked increase in the pulse rate, except in cases showing a very high temperature or pulmonary complications.

In every case that we have observed, the temperature during the course of the clinical manifestations of the thrombosis was 99° F. or over. Furthermore, in 70 per cent of our cases the temperature during the thrombosis rose to a higher point than it did during the first post-operative elevation. This has been an outstanding characteristic in all our cases. A typical temperature curve is shown in Fig. 1.

Most of the thromboses occurred during the second and third weeks of convalescence. The most common period is at the end of the second week, as is shown in our graphic curve of incidence. About 30 per cent of all of our cases of thromboses became evident in the 72 hours of the 12th, 13th and 14th days.

Pain is the first symptom to appear and also the first to disappear. Swelling follows the same rule and being the last symptom to appear, is also the last to depart. The convalescence of the patients is greatly prolonged by thrombophlebitis. The average stay in the hospital of these patients was 39 days, which is much longer than normal.

In spite of this prolonged convalescence, 63 per cent of our patients had symptoms referable to their thrombosis when discharged from the hospital. In most of these cases the symptom was swelling of the leg. In some instances, as is well known, this swelling persists for months.

Pulmonary Complications of Femoral Thrombosis.—The most serious complications of thrombophlebitis are pulmonary. In our series of 205, 14 patients (7 per cent) developed pulmonary infarcts, and three patients (1.5 per cent) pulmonary embolism. There were two deaths in this series, one patient dying of lung abscesses that developed in pulmonary infarcts, another of pulmonary embolism. Autopsies confirmed the presence of the thrombosis, infarction, lung abscesses and embolism. Two of the three patients with pulmonary embolism recovered, although the attacks were so grave as to be almost fatal.

As far as life is concerned, post-operative thrombophlebitis of the veins of the leg does not seem to be as serious as that of the pelvic vessels. This observation has been made before. In fact, it has become almost axiomatic that, of all types of post-operative thrombosis, that involving the femoral and saphenous veins is the most benign, particularly when accompanied with pain and swelling. The infrequency of death from pulmonary embolism in this type of thrombosis is indeed a remarkable fact.

The relatively benign course of this type of thrombosis has led some observers to draw rather sweeping conclusions. One reliable writer has stated that pulmonary emboli never have their origin from the saphenous vein. Such statements as this we cannot accept without reservation. Our own autopsy records, together with those of other clinics, show conclusively that fatal emboli may have their source in either the saphenous or femoral vein, in cases where there is pain and swelling of the leg as well as in those in which these clinical symptoms of thrombosis are absent. The fact remains, however, that fatal pulmonary embolism is not often associated with clinically evident thrombosis of the veins of the leg.

Pulmonary infarction is a more frequent complication of thrombosis than pulmonary embolism. In 7 per cent of our cases of thrombosis infarcts developed. That particles of thrombi are broken off and washed into the general circulation is evident from these statistics. Why they are rarely large enough to cause death from embolism is a rather difficult question to answer. The fact that we have kept all patients suffering from thrombosis in bed for a long period of time may perhaps have something to do with the infrequency of the development of embolism.

The treatment of thrombosis is very simple, chiefly because there is very little one can do. Twenty-five years ago the application of strong counter-irritants was in vogue. Legs were painted with iodine from Poupart's ligament to the heel. Then came the era of ichthyol and lead and opium liniments. In recent years our methods of treatment have become progressively simpler. We have discontinued local applications, as there may be danger in applying them too vigorously. Ice bags may be used locally, precaution being taken not to cause ice burns. Elevation of the leg will help the return flow of blood and ease the discomfort. Sedatives are indicated for the pain. We keep these patients in bed until the pain has disappeared and the swelling has practically subsided. It may not be superfluous to insist that massage in the treatment of post-operative pain in the legs is a dangerous procedure until the cause of that pain is known.

Pulmonary Infarction and Embolism

While we were studying the cases of post-operative thrombosis, our attention was attracted by the fact that a certain number of these patients developed pulmonary complications which to us clearly seemed to be due to infarcts. We noticed, moreover, that very few of these cases were diagnosed as pulmonary infarction; as a rule, they were called pleurisy or pneumonia. It therefore occurred to us to collect the cases diagnosed as post-operative pleurisy and see how many of them were primarily pleurisy and how many were infarctions. We did the same with the cases diagnosed as post-operative pneumonia, bronchopneumonia and bronchitis. And from the material collected in the study of 40 cases diagnosed as post-operative pleurisy, 80 cases as post-operative pneumonia and bronchopneumonia, and 50 cases as post-operative bronchitis, we have picked out 34 cases of undoubted post-operative pulmonary infarction. This number probably does not include all the cases we have had, for we have consistently eliminated all cases in which for any reason whatever the data were not sufficient to make a clean-cut diagnosis.

The study of infarctions of the lung naturally led us to include pulmonary embolism, for, in spite of essential differences, the two groups of cases are so closely associated as to

be inseparable, both clinically and pathologically. And both are likewise related to thrombosis. Thus we have seen cases of recognized clinical thrombosis repeatedly give rise to pulmonary infarction and attacks of infarction diagnosed as pleurisy and pneumonia followed later by fatal pulmonary embolism. Furthermore, without the information gained by the post-mortem examination of cases of pulmonary infarction and embolism, many clinical conclusions whose validity we have come to regard with some degree of assurance would hardly pass beyond the pale of impressionistic deductions.

The question naturally arises at this point: Why should the diagnosis of post-operative pulmonary infarction be so often missed, and on what basis do we feel warranted in assuming to question the diagnosis of other men—we who have never seen the patients and are merely looking over the records of these cases 10 to 25 years after the patients have left the hospital? After we have presented the cases of this series, we shall try to answer these pertinent questions.

The pulmonary complications associated with post-operative thrombosis fall into two main groups—pulmonary infarction and pulmonary embolism. A considerable amount of confusion has resulted from using these terms interchangeably. To avoid this, we shall roughly define these terms as we intend to use them. By infarction we mean the pathological and clinical picture following the dislodging of a thrombus, not large enough to occlude the blood supply of an entire lobe, but sufficient to occlude the artery supplying part of a lobe, giving rise to the characteristic picture of hæmorrhagic infarction of the area involved, and also causing the clear clinical signs and symptoms—sudden, sharp pain in the chest, increase in the pulse rate, elevation of the temperature, cough, dyspnœa, hæmoptysis, friction rub, râles, local impairment of the percussion note with change in the breath sounds, and more rarely cyanosis and shock. By embolism we mean the occlusion of the main trunk of the pulmonary artery or its principal branches by one or more emboli, giving rise to the grave picture so well known. Through our work we shall attempt to keep these two groups of cases distinct.

We present here the records of 51 different patients who had pulmonary infarction, pulmonary embolism, or both conditions. In these 51 cases, there were 34 instances of pulmonary infarction and 21 of pulmonary embolism. Of the 34 cases of infarction, five of the patients died; of the 21 cases of embolism, 19 patients died. We shall consider first the cases of pulmonary infarction, and then of pulmonary embolism.

PULMONARY INFARCTION

Pathology.—Post-operative hæmorrhagic infarction of the lung occurs most frequently in the right lower lobe. This has been noted by many observers and agrees with our findings. The primary seat of the thrombus is usually in the peripheral veins, or the pelvis. The infarct is cone-shaped, with the base out, producing a raised surface upon the visceral pleura, the apex of the cone pointing toward the hilum of the lung. The pleura in the earliest stage is still smooth and glistening, but soon becomes covered by a fibrinous deposit which gives rise to the friction rub heard in a majority of cases.

On section an infarct is solid, dark purplish-red in color, and generally presents a friable surface. The edges of an infarct are usually sharp and generally surrounded by an injected, inflammatory border. An old infarct may show signs of softening; in this case it is often gray in color.

Microscopically, the alveolar spaces are filled with red blood-cells, a few leucocytes, and are quite airless. The vessels leading to an area of infarction are found plugged by thrombotic emboli; the vessel walls may or may not show endarteritic changes.

Necrosis and cicatrization are rare. Absorption and re-establishment of the circulation usually take place through the pulmonary circulation in two or three weeks. With regard to this point, there is some difference of opinion, early observers claiming that resolution takes place through the bronchial system. When the infarction is due to infected emboli, abscess formation or gangrene may result. In one of our cases, a fatal pulmonary hæmorrhage occurred in one of these abscesses.

As a result of a series of careful experiments on pulmonary embolism and infarction, Karsner[10] and his collaborators make the following observation:

> **The same laws for mixture of the blood of the bronchial and pulmonary vessels, laid down in connection with the circulation in the lung in general, apply also to the circulation in an area of embolism, *i. e.*, there is no notable mixture of the bloods until the pressure in the one system or the other sinks to zero. Simple embolism of the pulmonary artery results in lower pressure in the embolic area, the pressure, however, not sinking to zero unless the blood supply of an entire lobe is cut off.**
>
> **With normal pressures in the two vascular systems an area of pulmonary embolism involving less than the entire lobe receives its blood supply almost entirely from the rich anastomosis of the pulmonary artery between its own branches, and only when the bronchial pressure is raised to an extremely high point does the blood from this vessel play a notable part in the circulation in the area.**

Zahn[11] demonstrated that passive congestion of the lung increased the likelihood of pulmonary infarction. This observation is in agreement with the work of Karsner, who reproduced this condition by tying the pulmonary vein or by compressing the lung by the introduction of sterile oil into the pleural cavity. In his experimental cases, Karsner found definite changes in the lung suggestive of infarction within three hours after the time of infarction and in 48 hours the pathological picture was complete. This is in accord with clinical observations. In practically all of our cases, no positive signs could be made out on the day of onset, while most cases showed a definite friction rub on the second day. According to Karsner's work, moreover, it required two or three weeks for the lung tissue to begin to function again after infarction.

These cases of sudden death which are produced by large "rider emboli" that obstruct both pulmonary arteries rarely show any pathological change in the lungs other than con-

gestion or œdema, unless the patient has had a previous infarction. This is illustrated by our autopsy cases.

The Clinical Picture of Pulmonary Infarction.—The first point we should like to present is the striking similarity between the clinical picture of the cases of pulmonary infarction and femoral thrombo-phlebitis, in regard to temperature and conditions of incidence.

With remarkable regularity, both conditions are found in the same type of patient and following the same type of operation. As regards age, infarction usually occurs before old age, only 1 case in 34 occurring above the age of 50 and 66 per cent of the cases between the ages of 20 and 40. Thrombosis shows the same age curve. Post-operative bronchitis and bronchopneumonia, on the other hand, are usually found in older patients.

As to the pre-operative condition, in 82 per cent it was good, in 18 per cent the patients were either anæmic, had a hæmoglobin of 65 per cent or less, or for some reason were not in first-class condition. Practically all, however, came under the group of good surgical risks. In 26 per cent some elevation of temperature was noted before operation; considering the fact that 18 per cent were operated upon for some inflammatory condition, this is quite to be expected.

Of these cases of infarction 48 per cent followed operations for myoma, 18 per cent salpingitis, 9 per cent retroposition of the uterus, 8 per cent carcinoma of the uterus, 6 per cent carcinoma of the rectum and hæmorrhoids; the remainder were equally divided between ovarian cysts, herniæ, appendicitis and kidney conditions. The operations performed were: Abdominal hysterectomies, 45 per cent; abdominal panhysterectomies, 6 per cent; vaginal panhysterectomies, 3 per cent; myomectomies, 6 per cent; operations on the adnexa, 12 per cent; suspensions of the uterus, 9 per cent; appendectomies, 6 per cent; the remainder followed kidney and rectal operations and herniotomies. These averages show a rather close correspondence with those of thrombosis, with the exception that we have had no cases of infarction following perineal operations. Clark goes farther than this in saying that thrombosis never occurs after perineal work. We have found that 8 per cent of our cases of thrombosis occurred after this type of operation, and have had cases of fatal pulmonary embolism after the same procedures. We should, therefore, be surprised if we do not either see or hear of cases of infarction associated with perineal operations.

With regard to the time of appearance of infarction, the same relation to thrombosis is evident; in 75 per cent it occurred during the second and third weeks, in 20 per cent after the third week, in 5 per cent during the first week, and none came on before the fourth day. Post-operative bronchopneumonia and bronchitis usually follow the operation immediately.

The convalescence before the onset of infarction was febrile in almost all the cases, the temperature varying consistently between 99° and 100° F. In only one case out of 34 was the temperature curve normal before the day of infarction. It is interesting that among the patients with infarction that showed no clinical evidence of phlebitis or femoral thrombosis, there was not a single case that had a clearly afebrile convalescence before infarction.*

Complications such as infected wounds and other conditions that might cause a post-operative elevation of temperature have been eliminated; hence we feel that this picture is fairly constant. Petrén has made this same observation with regard to embolism. Moreover, we believe it is what one might expect. In the type of case we are now considering, an infarction presupposes a thrombosis. Irrespective of the possible cause of thrombosis, we have found that a low febrile course precedes its manifestations in practically all instances; and that without exception in 205 cases there was a distinct elevation after the thrombosis became clinically evident. We feel, therefore, that the low protracted febrile course that precedes the infarction is due to the presence of a thrombosis.

After the infarction itself has actually occurred, the temperature curve shows a decided rise. As the clinical course of an infarction is usually short, in most cases a week suffices to see the temperature drop to its old level and most of the symptoms disappear. In a few cases the infarct is infected, and lung abscess or gangrene develops, usually with fatal results. In other cases, after the pulmonary signs and symptoms have cleared up, the temperature remains persistently between 99° and 100° F., or at times higher for two or three weeks. This temperature may be due either to the absorption of the infarct or to the thrombosis. The clinical significance of this type of temperature will be discussed later.

The interesting phase of the temperature curve is noted in the first few days. On the day of infarction the temperature is usually between 99° and 100° F.; in other words, it is not much higher than it has been continuously during the week or ten days before the infarction. It does not rise significantly until 24 hours after the infarction has occurred. We have noticed this in all but 2 out of 34 cases. Once elevated, the temperature curve is almost always of the hectic type, dropping in the morning and rising in the afternoon and evening. In these respects, infarction differs radically from the post-operative pneumonias, in which we have found that the temperature is distinctly elevated before the patient has any severe symptoms, rises progressively higher and is maintained at a high level. The second, third and fourth days of the infarction are usually the days of the highest fever, the temperature usually reaching 101°, at times 103° F. or more. The pulse usually accompanies the temperature, but the pulse curve seldom runs much above the temperature curve in ordinary cases.

The Signs and Symptoms of Infarction.—The symptoms that we have found in this series are striking. Pain on breathing is the outstanding feature. It has been present in every

* Since writing this article, we have had the opportunity of observing three cases of uncomplicated post-operative pulmonary infarction. In these instances the general picture of pulmonary infarction which we describe in this article was strikingly developed, in regard to both the temperature curve and the clinical course of the disease.

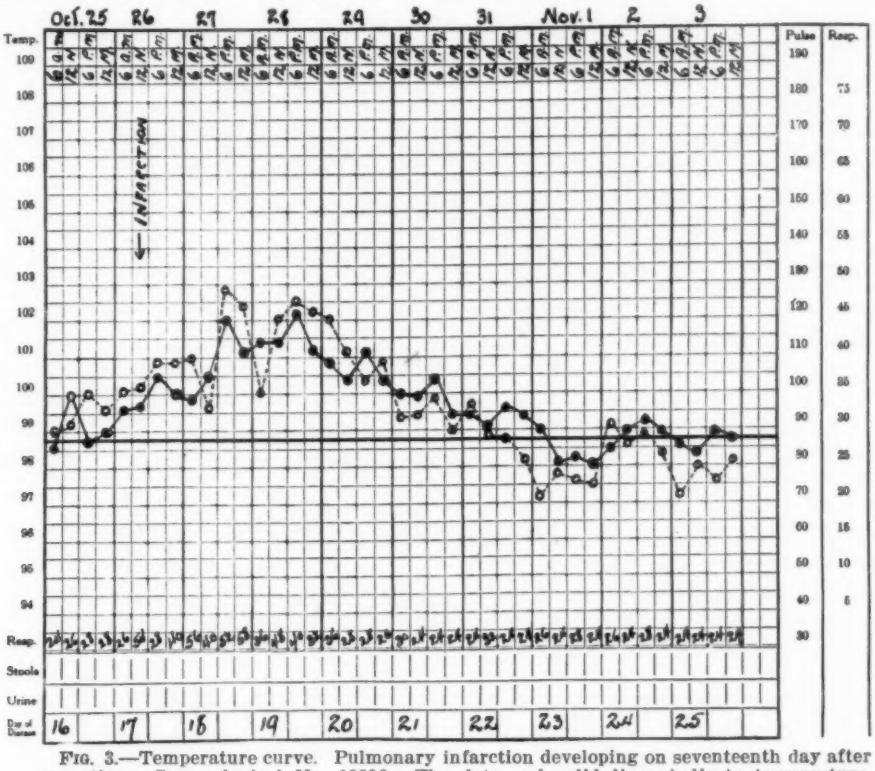

FIG. 3.—Temperature curve. Pulmonary infarction developing on seventeenth day after operation. Gynæcological No. 13296. The dots and solid lines indicate temperature. The rings and dashes indicate the pulse.

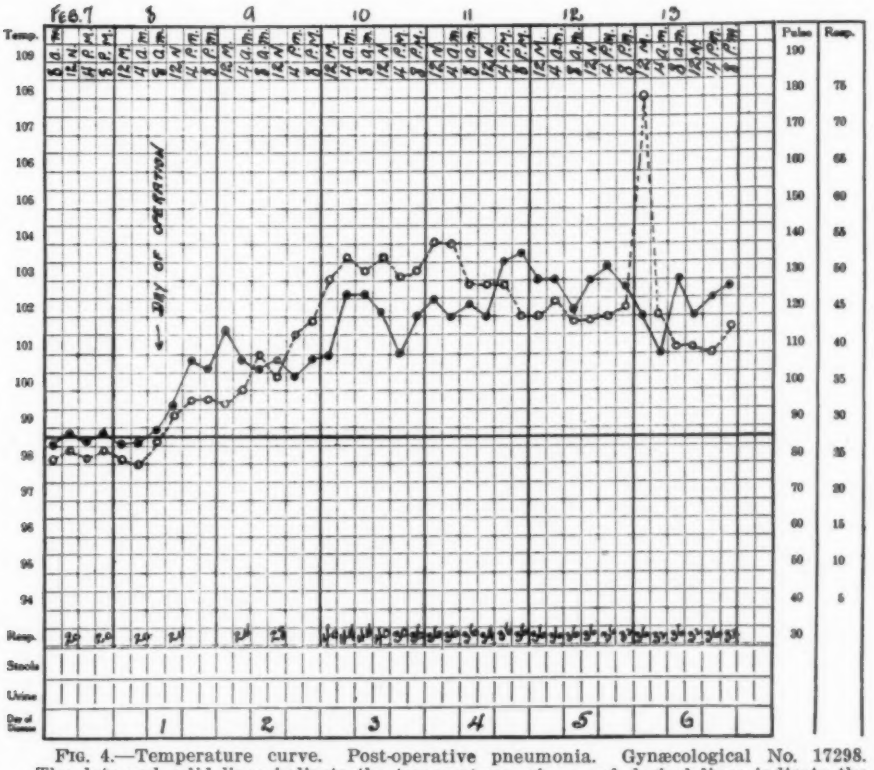

FIG. 4.—Temperature curve. Post-operative pneumonia. Gynæcological No. 17298. The dots and solid lines indicate the temperature; rings and dashed lines indicate the pulse.

one of our cases and has been the chief complaint. It is sudden in onset, usually very severe, making the taking of a deep breath almost impossible, requiring morphin frequently and in large doses. This pain is localized usually along the costal margin or over the lower ribs, usually in the axilla or below the scapula. In our cases, it was present on the right side four times as frequently as on the left. Both sides were simultaneously involved in two cases of this series. Pain is easily the first symptom in regard to time, prominence and regularity of appearance.

Compared with pain, cough is a rather minor symptom. One has to hunt through the histories to find the notes as to its presence. While we have found it in 63 per cent of our cases, when present it is usually not prominent, distressing or very productive. In this respect again, infarction differs from all types of post-operative inflammatory pulmonary complications.

Shortness of breath was present in 54 per cent of this series. It is usually not of the gasping, air-hunger type found in pulmonary embolism or severe secondary anæmia. The increased respiratory rate seems to be due chiefly to the inability of the patient to take a full deep inspiration without pain and the consequent substitution of a number of shallow respiratory movements. This symptom occurs on the day of infarction along with the pain.

Hæmoptysis we have found to be present in 36 per cent of our cases. If hæmoptysis be the *sine qua non* in the diagnosis of post-operative pulmonary infarction, as many text-books teach, we are afraid that two-thirds of the cases will be missed. Collapse and cyanosis are not frequent in infarction, unless the condition of the patient is extremely poor, or the infarction rather grave.

Anxiety and fear of impending death are not infrequently seen. The suddenness of the attack, the piercing thoracic pain and dyspnœa accompanied at times by sweats or chills, cannot but fail occasionally to produce a mental perturbation in a patient just recovering from a surgical operation.

Of the physical signs, the presence of the friction rub is the most characteristic. It has been noted in 75 per cent of our cases. Râles have been found in the same number, impairment of the percussion note and changes in the breath sounds in 63 per cent.

In the classical case of pulmonary infarction, the presence of all the characteristic symptoms and physical signs should make the diagnosis fairly certain. Unfortunately, however, these sign-posts are not always present. It is in such atypical instances as this, where there may be no friction rub or no hæmoptysis, that the clinical associations of pulmonary infarction come to our rescue and act as our guide. And these associated conditions, together with the immediate signs and symptoms, go to complete the clinical picture of pulmonary infarction.

We have already called attention to various factors in the clinical picture of infarction; its relation to the type of operation; the low febrile prodromal convalescence; the time of occurrence; its immediate clinical manifestations; and its usual course. The elements in the clinical picture which we would now present are: (1) Its association with femoral thrombophlebitis; (2) its association with repeated infarction; and (3) its association with pulmonary embolism.

Pulmonary Infarction and Femoral Thrombophlebitis.—We have noticed that pulmonary infarction and femoral thrombophlebitis are associated casuistically. They occur in the same type of patient, in the same age period, following the same groups of operations, in the same period of post-operative convalescence, and are preceded by the same low, continuous prodromal temperature. Our series shows, moreover, that the relation between thrombosis and infarction is closer even than this, for we have repeatedly found both complications in the same patient. In 41 per cent of our cases of pulmonary infarction there was venous thrombosis, with pain and swelling of the leg. In this group showing both conditions, the leg symptoms appeared before the pulmonary in 57 per cent of the cases. In 43 per cent the patients developed the infarction first, and a few days later pain and swelling of the leg appeared. We consider this clinical association to be strong confirmatory evidence in the diagnosis of pulmonary infarction.

Repeated Attacks of Pulmonary Infarction.—Although repeated attacks of pulmonary infarction in the same patient are not of every-day occurrence, they are not rare. In 10 per cent of our cases, the first infarction was followed by a second. We have no record of three distinct attacks of pulmonary infarction in the same patient. The time interval between attacks varied from 10 days to two weeks. In two-thirds of our cases, the second attack was more severe than the first. This is what one might expect, however, for in the short interval of 10 days, it is probable that in accordance with the recent experimental work of Karsner and Ash,[20] the lung tissue consolidated by the former infarction had not yet returned to normal function, and the subsequent sudden elimination of still another portion of the pulmonary reserve would naturally be accomplished by still greater reaction on the part of the patient. This is shown rather clearly by one case in which the second attack was all but fatal, although the physical signs that developed later seemed to indicate that the second infarction was limited entirely to the left lower lobe and apparently involved only a part of it.

Infarction and Embolism.—Infarction may be associated also with subsequent embolism. In this series of cases, embolism has occurred after infarction rather more frequently than a repetition of the infarction itself. In 12 per cent of our cases of infarction pulmonary embolism developed later, half of these cases of embolism being fatal. The time interval between the infarction and embolism varied from 10 days to three weeks.

In studying the records of the convalescence of these patients that had second attacks of either infarction or embolism superimposed upon an earlier attack, we noticed that the temperature had not fallen to normal in any case before the second supervened, even though there might have been an interval of three weeks between attacks. This is not the usual course of a case of pulmonary infarction. In a typical instance, the tempera-

ture commences to drop on the fourth or fifth day after infarction; in 10 days it is either normal or very nearly so and the symptoms have entirely cleared up. Careful examination of the chest may show a residuum of only a few physical signs.

An elevation of temperature persisting for over a period of two weeks following an infarction usually means a complication. Our commonest complications have been lung abscess, bronchopneumonia, pulmonary gangrene, miliary abscesses and septicæmia. All of these usually give definite symptoms which immediately offer a clue in discovering the cause of the fever. But excluding cases with these complications, all of our cases of repeated infarction or embolism showed between the attacks a definite persistent pyrexia, seldom exceeding 100° F. During this interval these patients have absolutely no discomfort, no localizing signs and no symptoms explanatory of the elevation. We believe that the association of this unexplained elevation of temperature with cases of repeated infarction and embolism indicates that the same conditions which gave rise to the primary infarction are still present and active, and under certain circumstances might lead to the same results again.

The relation of the temperature to thrombosis and embolism has been emphasized before. Two foreign observers have confirmed our findings in this respect. In 1912 Michaelis [1] stated that "post-operative and post-partum thrombosis and embolism do not occur wholly without premonitory signs; if the temperature is taken frequently and accurately enough, one will observe a low febrile temperature before the onset of these complications. In a patient that does not have this low elevation, we do not need to fear the possible development of thrombosis or embolism." Petrén supports Michaelis in his clinical observations, but does not indulge in prophecy.

On the basis of our series of cases, we believe we can make the same application to infarction and particularly to cases of repeated infarction or embolism. Although we would not go so far as to say that patients who have a perfectly normal temperature during convalescence will not develop thrombosis, infarction or embolism, yet we feel that the presence of a persistent, low, unexplained fever late in convalescence should make one think of these complications. By way of illustration, we might cite as a rather typical case, a patient who on the 12th day had a mild attack of post-operative infarction which was diagnosed as pleurisy. In a week her symptoms had cleared up completely, and at the end of two weeks, the physical signs in the chest were negative. She still had an elevation of temperature reaching 100° or 101° F. every night, with no localizing signs or symptoms. Her sputum was examined for tubercle bacilli, her operative wound had healed, she had no pain or swelling of the leg, and no cause for the elevation was found. As she was feeling perfectly well, she began to chafe under confinement in bed, and demanded that she should be allowed to go home. On the 21st day after her infarction, she was therefore discharged from the hospital, and while walking around the ward telling the patients goodbye, had a fatal attack of pulmonary embolism, dying almost instantaneously.

These cases emphasize two points: (1) The importance of diagnosing pulmonary infarction; and (2) the necessity of keeping patients who have had a pulmonary infarction in bed until their temperature is normal. We would not presume to state that pulmonary embolism can be avoided by keeping patients in bed, for our records show that many cases of embolism occur in the first week of convalescence; moreover, patients well along in convalescence have had an embolism during the night while merely turning over in bed. On the basis of these records, however, we feel certain that the presence of a low febrile temperature for two or three weeks following an infarction should be a distinct indication to keep that patient as quiet as possible until the temperature is normal, or until a definite cause for the elevation has been established.

Causes of Death in Pulmonary Infarction.—Pulmonary infarction in itself usually runs a short course and the patient recovers. Because of its occasional association with serious complications, however, it may take a more grave aspect.

These complications are due to: (1) Septic emboli, which give rise to infected infarctions; (2) bland infarctions in a lung already infected; and (3) second attacks of either pulmonary infarction or embolism.

Of our 34 cases of infarction, in five the patients died, a mortality of about 15 per cent. The causes of death in these cases were:

Gangrene of the lung	2 cases.
Abscess of the lung, uncomplicated	1 case.
Abscess of the lung with terminal pulmonary embolism	1 case.
Pulmonary embolism, uncomplicated	1 case.

All but one of these five cases came to autopsy. The only one that was not examined post mortem was a case in which death had occurred from a typical pulmonary embolism three weeks after the day of infarction. The terminal event of one of the cases of gangrene was an intrapulmonary hæmorrhage, due to the necrotic perforations of the vessels in the gangrenous lobe. Lung abscesses due to septic emboli are often associated with septicæmia and metastatic abscesses in the liver, spleen and kidneys. At the close of the article we shall include detailed reports of cases representing each of the above types of infarction.

As a rule, attacks of infarction occurring during the first week of convalescence are apt to be more serious than those that develop later. During the first few days after an operation, the general resistance of a patient is low and a small embolus might produce a degree of shock out of all proportion to its size. Then again, for several days after an ether anæsthetic, the lungs may be irritated, slightly congested and there may be a mild bronchitis. An infarct in such a lung might furnish an ideal culture medium in which a low grade infection might develop into full virulence. It is noteworthy that in this series of cases, in half of the patients that died of pulmonary abscess or gangrene the infarctions had appeared definitely before the sixth day after operation. In the remaining patients that died of these complications, it was impossible to fix the exact date of infarction.

The Treatment of Pulmonary Infarction.—The treatment of pulmonary infarction is symptomatic and expectant; symptomatic in that nothing radical can be done to cure the infarction; expectant in watching the developments of the case and attempting to prevent further complications.

The symptoms which require therapeutic attention are pain, dyspnœa, cyanosis, shock, anxiety and restlessness. Cyanosis and shock are rarely present, and the cough is not often distressing. For the pain, morphin is strongly indicated. We see no reason why it should not be given in sufficiently large dosage to keep the patient as quiet as possible. Strapping of the chest by broad strips of adhesive may relieve the pain by mechanically lessening the pleural movements on the side affected.

Dyspnœa is usually present, often in ratio to the severity of the pain. The relief of the pain will lessen the dyspnœa. Fowler's position may make the respirations easier. When the dyspnœa is accompanied by cyanosis, it usually means real insufficient oxidation of the blood, and requires active therapy. In this type of case, oxygen may give instant relief not only in clearing up the cyanosis, but also in lessening the respiratory rate. This in turn relieves the patient of exhaustion, rests the heart, lowers the pulse rate and calms the restlessness and anxiety of the patient. Fresh air is also of value for the same reason. Of drugs, we have combined atropin with morphin, especially in the presence of a productive cough; strychnin, strophanthin and caffein are also useful. It is not often, however, that a case of infarction requires such active stimulation.

The anxiety and restlessness of the patient may be out of all proportion to the severity of the lesion. These must be controlled, as the danger of secondary infarction or embolism is always present. Rest is essential, and for this purpose the treatment we have outlined above is our chief reliance. In addition to this, firm assurance and encouragement may play no small part in helping the patient over the critical period of her convalescence.

After the first 48 hours, the acute symptoms usually disappear and we pursue a course of expectancy. If the temperature falls to normal after 10 days or two weeks, we feel assured that the greatest danger is past and that the infarct is resolving normally without complications. If, however, pulmonary symptoms continue, the temperature mounts steadily higher and the physical signs accumulate rather than disappear, we probably have to deal with an infected infarct and this is usually a serious matter. In our series, this happened in 10 per cent of the cases.

Usually, however, the infarction pursues its short course, the pulmonary symptoms clear up in about a week, the signs may linger a week or 10 days longer and with their disappearance the temperature reaches normal. After this event, we tentatively let the patient up in a chair. If no accident follows, we allow her to walk, and in a day or so she goes home. As we have stated before, we can in no way indorse the practice of letting patients out of bed following pulmonary infarction until the temperature is distinctly normal. This is a hard rule to enforce, as patients, who have no symptoms and feel perfectly well, chafe under prolonged confinement. It is, nevertheless, the only safe rule to follow.

The Recognition of Pulmonary Infarction in Clinics Other Than Our Own.—It is needless to say that we were surprised when we observed the almost regular consistency with which the diagnosis of pulmonary infarction has been missed in our own clinic. Only 10 per cent of our cases have been recognized. We, therefore, examined the literature, the recent text-books and the reports of other large clinics to see whether this complication was being recognized elsewhere, for "Misery likes company."

The literature on post-operative thrombosis and embolism practically always mentions infarction as a possibility. This is particularly true of the foreign articles. In the case reports of post-operative pulmonary complications, however, there seems to be a marked silence with regard to the subject. Standard text-books seem to ignore it. One large volume published recently, in devoting almost a thousand pages to surgical after-treatment, does not mention it. Infarction is not even found in the index. In 1913 and 1917, respectively, rather extensive articles appeared in the medical literature, reporting, in detail with case histories, the post-operative pulmonary complications in two of the largest and most up-to-date surgical clinics in America. Extensive bacteriological studies in the various types of post-operative pneumonias were reported, but not a single case of pulmonary infarction is mentioned. It is true that the author of one of these articles made the statement that small emboli might possibly be the cause of some post-operative pulmonary complications, but in not one instance is the diagnosis of pulmonary infarction made. All these cases were diagnosed either as pneumonia, bronchopneumonia or pleurisy. In looking over these reports in detail, we feel certain that some of the cases were undoubtedly pulmonary infarctions and should have been so diagnosed. Furthermore, if the reports of these two large clinics, together with our own, show such records as this, it is highly probable that the profession at large is no more wide-awake to the true nature of the complication.

The Diagnosis of Pulmonary Infarction.—In our clinic the diagnosis of pulmonary infarction has been anything but good. We have recognized only 10 per cent of our cases. What is the explanation of such a poor record? The answer is simple—the diagnosis had been based practically always upon the physical findings in the thorax instead of the whole clinical picture.

Let us consider, then, the different items that constitute the clinical picture in one of these cases.

Class of Case: To begin with, we are dealing with a post-operative patient who is convalescing from a laparotomy, frequently a hysterectomy.

Time of Occurrence: This complication occurs practically always in the second or third week after operation.

Temperature: The temperature curve is quite characteristic when not complicated by other factors. The patient has a low unexplained evening temperature of 99° to 100° F. after operation. After the day of the infarction, the temperature rises sharply, but seldom goes much above 102° F. The curve is hectic in type, not like that of pneumonia. It reaches its highest point between the second and fourth days and usually drops almost to normal again at the end of a week.

Attack: Infarction almost always makes its appearance in an acute attack with sharp sticking pain over the ribs as the dominant symptom. The attack may be accompanied by a definite chill; this, however, is rare. Chilly sensations are not infrequent.

Leucocyte Count: This usually varies between 12,000 and 18,000, and is of little help in the diagnosis.

Physical Signs: The physical signs rarely make their appearance before the second day. The most constant of these is the friction rub, which was noted in 75 per cent of our cases. It probably is present in a greater number, but this represents only those cases in which it was noted upon the history. Râles were heard in 75 per cent of our cases; they are usually evident a little later than the friction rub. Impairment and changes in the breath sounds appear last and were noted in 63 per cent of our cases.

Symptoms: Pain ushers in the attack and is always the predominant symptom. Cough, while present in 63 per cent of our cases at some time, is usually not severe, and in most cases is unproductive. Hæmoptysis was present in 36 per cent of our cases and when present, practically clinches the diagnosis. Phlebitis, pain and swelling of the leg occurred in 41 per cent of this series, and when present is just as confirmatory as hæmoptysis.

A Typical Case of Pulmonary Infarction.—It might be of interest to describe a typical case of pulmonary infarction. Let us take a well-nourished woman 40 years of age, who has had a hysterectomy for a myomatous uterus. She is returned to the ward in good condition, has a slight post-operative reaction and then settles down to a satisfactory convalescence. The wound is dressed by the ward surgeon, found to be clean and the stitches are removed. On account of a slight daily rise of temperature to 99.5° F., he examines the wound very closely for stitch infection. The patient continues to improve, has no discomfort, and is allowed to be up on the 14th day. Suddenly she is seized with sharp pain in her right side, more especially on deep inspiration. The nurse promptly returns her to bed and takes her temperature, finding it to be 100° F. The ward doctor is informed, makes a careful examination of the chest, but finds nothing definite. The patient is reassured and forgotten. On the following morning, in making his rounds, the doctor is informed that his patient still complains of pain in her right side and that her temperature is 102° F. He goes over the chest promptly, finds a friction rub, with a few râles below the angle of the scapula and makes a diagnosis of dry pleurisy. A day or two later the patient may develop hæmoptysis or phlebitis of the leg. She usually makes a prompt recovery and in 10 days the little pulmonary upset is a thing of the past and forgotten.

Differential Diagnosis.—The conditions from which pulmonary infarction must be differentiated, named in the order of their frequency, are: Pleurisy, pneumonia, pulmonary tuberculosis, bronchitis, empyema, gangrene of the lung, pulmonary abscess and subdiaphragmatic abscess.

Of the cases diagnosed as post-operative pleurisy in this clinic, we believe that 45 per cent were infarctions. Of course, we realize that these patients did have a fibrinous pleurisy so that in a way the diagnosis was correct. The important fact, however, that the pleurisy depended upon an infarct, was overlooked. A dry fibrinous pleurisy of other origin would be hard to differentiate and the diagnosis would depend upon the later development of consolidation or hæmoptysis. Serofibrinous pleurisy should be easily differentiated by the presence of the pleural effusion and exploratory puncture with the needle. A previous history of tuberculosis would be helpful. Many cases of criminal abortions and severe puerperal infection develop pleurisy, generally associated, however, with peritonitis, pneumonia or metastatic lung abscesses.

Pneumonia might offer difficulties in the early stages, but when the clinical picture is complete, it should be readily differentiated. Of our cases 12.5 per cent diagnosed as post-operative pneumonia were due to pulmonary infarctions. The onset of pneumonia is usually immediately after the operation, the temperature rises quickly and is sustained. Cyanosis is more marked, the leucocyte count higher and the sputum usually rusty instead of bright red. The course of pneumonia is more severe than that of a simple infarction, and the patient is distinctly more toxic.

An old latent tuberculosis lesion in the lung is not an infrequent cause of trouble in operative cases. These patients may show a reactivation of their old process; it usually takes place very soon after operation; the temperature curve may be very irregular; there is generally a profuse muco-purulent expectoration against little or no expectoration in infarction. The presence of hæmoptysis in infarction almost always makes one think of tuberculosis, and in many of our cases tubercle bacilli were repeatedly searched for. The finding of the tubercle bacilli, the location of the apical pulmonary lesion, the history and X-ray should aid in clearing up the diagnosis.

In our cases bronchitis apparently offered no confusion in diagnosis, for none of our infarctions were mistaken for this condition. The absence of pain and friction rub, the presence of a profuse expectoration with a distressing cough, the onset immediately after operation, the low temperature and different physical signs, usually separate these cases clearly.

Empyema, lung abscess and gangrene of the lung occasionally develop in infected infarcts. The onset of infarction should serve to show the true nature of the complication. Empyema, however, more often follows pneumonia and should not be confused with a simple infarct. Post-operative gangrene of the lung may also follow pneumonia or the

aspiration of foreign material. The history, sputum and X-ray should clear up the diagnosis. Subdiaphragmatic abscess should be differentiated on the basis of abdominal symptoms and the X-ray. These patients are also usually more toxic than those suffering from infarction.

What right have we to make a diagnosis of pulmonary infarction upon the basis of the clinical records without even having seen these patients? We feel that it cannot be done in all cases, and consequently have rejected many cases in which the data seemed to be insufficient. The diagnosis, we repeat, must be based upon the complete clinical picture and not upon the physical findings alone.

Let us subject our 34 cases of infarction to a brief analysis. Out of these 34 cases, in only 12 was there neither hæmoptysis nor phlebitis. We assume these conditions to be very strong confirmatory evidence where a clinical picture of infarction exists. Of these 12 patients five died; in four of these autopsy proved the presence of the infarct, the fifth died of typical pulmonary embolism. Of the remaining seven, one had two typical attacks separated by an interval of one week. In the remaining six cases we were not aided by the presence of hæmoptysis or phlebitis, but based our diagnosis upon the history of typical attacks occurring between the 9th and 18th days with the usual physical findings and characteristic temperature curve.

Post-Operative Pulmonary Embolism

We shall now conclude by mentioning the cases of pulmonary embolism we have encountered. There is such a wide literature on this subject that we shall attempt to bring out only two points: (1) The relation of pulmonary embolism to pulmonary infarction and thrombophlebitis; and (2) unusual symptoms that may be found in pulmonary embolism.

We have had 21 cases of pulmonary embolism in this series. As we have stated before, we separated them from the cases of infarction because both pathologically and clinically they offer certain marked points of difference, though at basis they have the same etiology.

The Pathology of Embolism.—Of 19 cases of fatal pulmonary embolism, all but two came to autopsy. These two patients died in attacks that were clinically absolutely typical.

From the pathological viewpoint, there is very little similarity in the appearance of a lung the site of a pulmonary infarct and a pulmonary embolus. The lungs of a patient dead of sudden pulmonary embolism rarely show any lesion beyond œdema and congestion. We have never observed the picture of hæmorrhagic infarction in any of these cases unless the patient has had an infarct before the fatal embolism occurred. Occasionally there has been a moderate hydrothorax and a slight increase in the quantity of pericardial fluid. Dilatation of the right heart and of the superior and inferior vena cava is usually marked.

In case a patient lives several hours after embolism, patches of bronchopneumonia may be found in addition to the œdema. We have found the usual source of pulmonary emboli to be the pelvic veins; in 15 per cent of our cases the origin was in the veins of the leg.

There is a border-line group of cases that we have not had the opportunity of studying pathologically. We refer to the cases in which there were large emboli, but of insufficient size to cause death. At the onset of the attack these cases present the typical clinical picture of grave pulmonary embolism. Within two or three days, however, the signs of infarction come to the fore.

We have had two such cases and from them have been able to gather a rather interesting symptomatology. Pain is almost not felt in these attacks. Although death from pulmonary embolism is always tragic, it is probably almost painless. The chief complaint of these patients has been a feeling of immense weight in the substernal region of the chest, which seemed to make it impossible for them to breathe. While the point has almost no clinical value, it is to be noted that most patients showing this symptom die.

The Occurrence of Pulmonary Embolism.—Although pulmonary embolism may follow almost any type of surgical procedure, it is usually associated with laparotomies. One of our cases occurred during the convalescence after closure of a vesico-vaginal fistula.

Pulmonary embolism may occur at any time during convalescence. It is apt to happen earlier than either pulmonary infarction or thrombophlebitis. One of our patients had a fatal attack three hours after operation, another at the end of 24 hours. Half of our cases developed within the first six days; practically all of the rest of them during the second week.

Pulmonary embolism is much more serious, of course, than pulmonary infarction. Fifteen per cent of our cases of infarction died; 90 per cent of our cases of embolism. Both groups of cases almost uniformly show a low febrile convalescence up until the day of infarction or embolism. In 80 per cent of our cases of embolism there had been a daily unexplained rise in temperature, reaching at least 99.4° F. until the day of embolism. In some cases the temperature had been as high as 101° F. every day for a period of 10 days or more before the attack.

We have seen that a patient may have repeated attacks of pulmonary infarction and that the second is usually more serious than the first. Repeated attacks of pulmonary embolism are not so common, principally because the first is almost always fatal. Three of our patients apparently died during second attacks of pulmonary embolism, the second attack being superimposed upon the first after an interval of from 1 to 15 hours. No patient survived the second attack of embolism.

Pulmonary Embolism and Thrombophlebitis.—The relation between thrombophlebitis and pulmonary embolism is not as clear as it might be. It seems to be an established fact that pulmonary embolism does not often occur in patients who have pain and swelling of the leg. Out of a group of 205

patients who showed clinical signs of thrombophlebitis, we have had only three cases of pulmonary embolism. On the other hand, in this same group there were 14 instances of pulmonary infarction. In only 10 per cent of our cases of pulmonary embolism were there pain and swelling of the leg, whereas in almost half of our cases of infarction they were present.

The infrequency with which pulmonary embolism is associated with pain and swelling of the leg is brought out more strikingly yet by this series. Out of 21 cases of pulmonary embolism in only three had there been a thrombophlebitis, and two of these three patients are the only ones that suffered from pulmonary embolism that did not prove fatal. In other words, we have had only one single fatal case of pulmonary embolism in 205 consecutive cases of thromboplebitis. These represent all the cases of thrombophlebitis following 21,000 gynæcological operations—a rather remarkable record.

Why these two conditions are not more frequently associated is rather difficult to explain. We have heard of very little experimental work having been done to clarify this situation. Reasoning from a purely clinical basis, however, it seems to us that the explanation for this phenomenon is apt to be found in the nature of the thrombophlebitis with which we are dealing. If traumatism and infection are the chief causes of thrombosis, femoral thrombosis associated with pain and swelling seems to us to show the characteristics of an inflammatory process. All the cardinal signs of local inflammation are present in a typical case of this sort. There is pain along the course of the femoral vessel and also in the leg; swelling is present, local tenderness is usually noted; the surface temperature is often elevated; even redness of the skin in the region immediately surrounding the thrombus may be present. Whether, as a result of this evident inflammatory reaction, the thrombus becomes so adherent to the vessel wall that it cannot often be dislodged, is a mere supposition of ours that needs further confirmation.

On the other hand, it seems probable that traumatic and mechanical factors play a larger part in the formation of pelvic than in this type of femoral thrombosis. The inflammatory picture is not striking in the cases of pelvic thrombosis with embolism, as it is in femoral thrombosis with pain and swelling of the leg.

It is rather difficult to carry this analogy from the femoral vein to the veins of the pelvis, for the anatomical situation of the iliac and the ovarian plexus makes the symptomatology associated with their thrombosis somewhat obscure. For this reason the diagnosis of pelvic thrombosis is almost never made clinically; it is usually recognized only on the operating table or at autopsy. Consequently, it would be very difficult to make a clinical differentiation between inflammatory and traumatic types of pelvic thrombosis in their relation to pulmonary embolism.

There are, nevertheless, certain clinical facts which lead us to believe that traumatic thrombosis of the pelvis veins is more often associated with embolism than the inflammatory type. Autopsy records show that in 85 per cent of our cases of fatal pulmonary embolism the origin of the embolus was in the pelvic veins. In these cases, the thrombosis was symptomless. It caused no discomfort whatever. This is in rather sharp contrast with the severe pain associated with femoral thrombosis. In the second place, pelvic thrombosis associated with embolism is apt to occur earlier in convalescence than femoral thrombosis with pain and swelling of the leg. Half of our cases of embolism occurred during the first week of convalescence, two within 24 hours after the operation. Femoral thrombosis almost never occurs as early as this. This may indicate a different etiology. In the third place, thrombosis of the pelvic veins in severe pelvic inflammatory disease without operation almost never gives rise to embolism. In these cases of thrombosis there has been no operative trauma and it seems that the thrombosis must be purely infectious in origin. This type of thrombosis is seen not infrequently on the operating table in the presence of very extensive and severe pelvic inflammatory disease, with cellulitis of the broad ligaments. In these cases one may at times cut across a broad vascular base with almost no bleeding, owing entirely to the inflammatory thrombosis of the vessels. Yet sudden death from pulmonary embolism occurring before operation is almost unheard of in connection with pelvic inflammatory disease. In the fourth place, the mechanical factors conducive toward thrombosis are very marked in the pelvic vessels. These veins are large, tortuous, are directly subjected to the trauma of the operation, are clamped and ligated. Autopsy shows, moreover, that in a considerable proportion of these cases, no gross evidence of infection can be found.

While the above evidence seems to point toward traumatic thrombosis as the usual cause of pulmonary embolism, we would not for a moment state that thrombosis with inflammatory signs cannot cause embolism. For in definite instances, as we have shown, clinical and pathological evidence points to quite the contrary view. This, moreover, is what one would expect. Infection and trauma are both involved in the etiology of venous thrombosis, and just so far as the clinical differentiation of these two types of thrombosis is not clear, to that extent we must admit that it is impossible to associate the occurrence of pulmonary embolism with either type in any definite causal relationship. Cultures from large amounts of centrifugalized blood taken from patients exhibiting symptoms of phlebitis and infarction might show an increasing number to be associated with infection. The solution of this question might possibly lie in the routine microscopic and bacteriological examinations of the thrombus, the vessel wall and the surrounding tissues. Unfortunately, the records on this phase of the question are insufficient to make any valid deductions. Until some such co-ordinated study as this is done on the clinical and pathological aspects of the venous thrombosis and pulmonary embolism, we feel that the final explanation of these problems will remain in abeyance.

The Diagnosis of Pulmonary Embolism.—Pulmonary embolism is usually not difficult to recognize. This is especially true in the typical case in which death occurs very soon after

the onset of symptoms. As about 50 per cent of our patients died within 30 minutes, the diagnosis offered but little confusion. Pulmonary embolism, however, is neither always fatal nor even rapidly fatal. In 25 per cent of our cases the patients lived as long as an hour after the beginning of the attack, and in 15 per cent from 15 to 24 hours. In 10 per cent there was complete recovery.

The chief diagnostic interest centers about that group of cases in which death is deferred for some time after the onset of the attack. During this period of from 15 to 24 hours, the most varied and remarkable clinical pictures may develop. As a result of this, these cases have been mistaken for cerebral embolism, intracranial hæmorrhage, epilepsy, hysteria, post-operative shock and intra-abdominal hæmorrhage.

When we consider the type of lesion with which we are dealing, this confusion of symptoms leaves little cause for wonder. On the basis of the pathology of pulmonary embolism, almost any clinical picture can be explained. The sudden and more or less complete occlusion of the pulmonary artery to all intents and purposes immediately eliminates oxidation of the blood, mechanically cause a dilatation of the right heart and engorgement of the superior and inferior vena cava, acute congestion and stasis of the blood supply in the abdominal viscera, the brain and extremities. Such a complete vascular disorganization as this at once produces the most profound shock, asphyxiation of the tissues and a host of secondary disturbances of the entire nervous system. Furthermore, in patients who have developed thrombosis of the pelvic plexus or the femoral vein, there might also be a concomitant thrombosis in some unusual location, as we have seen in this series of cases. It is quite possible that in no small number of instances unusual symptoms might be due to the occlusion of a vessel which is not commonly the site of post-operative thrombosis; for example, in the portal or the cerebral circulation. These anatomical and physiological changes give rise to the grave picture of pulmonary embolism, its overwhelming collapse, dyspnœa, cyanosis, rapid, thready and irregular pulse, neurological and abdominal manifestations and usually a fatal termination.

Bearing in mind the variety of physiological disturbances that accompany pulmonary embolism, we may readily understand the various clinical manifestations it may take, provided the patient lives long enough to develop them. The atypical symptoms which we have observed most frequently fall into two groups: first, neurological; second, abdominal.

In the first group of cases, of which we have three, the localizing symptoms were chiefly cerebral. Crossed paralyses, spasticity or twitching of the muscles of one side of the face, irregularity of the pupils, ocular deviations, heavy and inarticulate speech, general epileptiform convulsions interspersed with intervals of deep coma have all been noted in these cases. Sometimes the pulse may become full and strong after the initial shock of the attack has passed away. As a terminal event, the temperature may rise rapidly to 104° or 105°F. In this type of pulmonary embolism, especially when associated with hypertension and advanced age, the idea of intracranial hæmorrhage or cerebral embolus might readily be entertained.

In another group of instances the abdominal symptoms predominate. We have seen two of this type. In cases of this character, abdominal pain, distension, tenderness, nausea, vomiting, a weak and thready pulse and cold extremities might readily lead one to think of intra-abdominal hæmorrhage or post-operative obstruction. At the close of this paper will be found the detailed report of one case of this character that was seen by the chiefs of two departments and operated upon for intra-abdominal hæmorrhage. The possibility of embolism was considered, but hæmorrhagic shock seemed to be the prevailing view. Fortunately, this patient survived both the operation and embolism. Embolism may simulate post-operative shock, particularly when it occurs early in the convalescence and in a patient in poor condition.

All but one of these patients with atypical symptoms died, and autopsy revealed an uncomplicated pulmonary embolism. The only patient that lived was the one that was operated upon for intra-abdominal hæmorrhage. This possibility was eliminated by the operation and the diagnosis of pulmonary embolus was made on the pulmonary picture which developed, the fact that two weeks before the embolism this patient had a typical pulmonary infarction which was diagnosed as pleurisy, and that two days after the second operation she developed femoral phlebitis.

These cases merely go to show that whatever aids can be brought to bear in the diagnosis of post-operative pulmonary complications clarify the view and place post-operative treatment on a more rational basis; after all, it is the clinical picture as a whole that counts, usually far more than any single physical finding. This paper has been virtually a post-mortem examination of the mistakes that have been common in the diagnosis of post-operative pulmonary conditions; and while post-mortems are at times embarrassing, they still have their advantages. In this article we have attempted to point out a few of the main clinical features of a group of post-operative pulmonary complications that have heretofore usually passed unrecognized. This we have done in the hope that, if recognized, these complications may be treated in a more satisfactory manner and, if possible, their more serious sequelæ avoided.

Conclusions

1. Post-operative venous phlebitis and thrombosis are not peculiar to any particular type of gynæcological operations.

2. There are a number of conditions that favor thrombus formation. Of these, we feel that infection and trauma play the most important part.

3. Perineal operations are not free from these complications.

4. Practically all cases of thrombophlebitis are associated with a slight rise in the temperature curve.

5. Phlebitis and thrombosis of the leg veins when associated with pain and swelling are rarely ever followed by fatal embolism.

6. Pulmonary infarction occurs most often in the same class of cases and during the same period of convalescence as femoral thrombophlebitis.

7. Pulmonary infarction may precede pulmonary embolism.

8. Post-operative pulmonary infarction in the majority of cases has heretofore been unrecognized.

9. The diagnosis of post-operative pulmonary infarction must be based on the clinical picture rather than the physical findings alone.

10. We believe that with proper care, pulmonary infarction should be diagnosed.

NOTE.—Since the completion of this paper our attention has been called by Dr. Howard A. Kelly to a short article on this subject published in 1902 by Dr. G. Brown Miller,[23] formerly resident gynæcologist of this hospital. After reviewing a series of 16 cases which had been diagnosed as post-operative pleurisy, he arrived at the conclusion that eight of them were primarily due to pulmonary infarction. Seven of these eight cases are included in our series; the eighth case, which Dr. Miller presented, we have not included, because we felt that the data were insufficient to make a diagnosis. Dr. Miller himself stated that he was not certain that this case was one of infarction.

That two groups of observers, separated by 17 years, should independently pick out the same cases from a large number of post-operative pulmonary complications and reach the same conclusions, is a rather unusual coincidence. Even though Dr. Miller presented but a small series of cases and did not have the opportunity to establish any of his impressions by autopsy confirmation, it must be stated that he presented a clean-cut clinical picture of pulmonary infarction and was probably one of the first to call attention to the frequency with which it is confused with pneumonia and pleurisy. We are in complete accord with many of the opinions which he advanced.

CASE REPORTS

1. Gyn. No. 8222. Fatal pulmonary embolism with previous infarction.

2. Gyn. No. 3492. Atypical pulmonary embolism with abdominal symptoms. Previous infarction. Embolism diagnosed intra-abdominal hæmorrhage. Exploratory laparotomy. Femoral thrombosis following embolism. Recovery.

3. Gyn. No. 24894. Atypical pulmonary embolism with cerebral symptoms. Autopsy No. 5920.

4. Gyn. No. 13296. Typical case of bland pulmonary infarction. Recovery.

5. Gyn. No. 12587. Pulmonary infarction, multiple. Secondary lung abscesses. Death. Autopsy No. 2651.

6. Gyn. No. 17670. Pulmonary infarction. Gangrene of lungs, with terminal pulmonary hæmorrhages. Death. Autopsy No. 3585.

CASE 1.—*Gyn. No. 8222. Fatal pulmonary embolism with previous infarction.*

Mrs. H., aged 27. One child.

Complaint.—Pain in epigastrium, with attack of indigestion.

Diagnosis.—Retroposition of uterus. Laceration of perineum.

Operations.—October 17, 1900. Suspension of uterus. Perineorrhaphy. Gall-bladder and pylorus negative.

Post-Operative Notes.—October 21, 1900. Condition of patient good. Has been having a slight elevation of temperature; perfectly comfortable.

October 23, 1900. Stitches removed. No pain in abdominal wound. No evidence of inflammation in pelvis. Wound in excellent condition. Temperature still slightly elevated.

October 28, 1900. For the last few days the patient has complained of pain in her lower right side, just below the costal margin, extending around to the back, sharp and shooting, not in the gall-bladder region. No definite tenderness on pressure. Slight hypersensitiveness of the skin. The Pacquelin cautery relieved the pain for a short time.

November 3, 1900. Medical consultation. Patient's respiration rather rapid, superficial. Deep inspiration causes severe pain. No herpes. Pulse 28 to the quarter; no expectoration. Lungs: right side; vocal fremitus is a trifle diminished over the lower right lobe. Throughout the area corresponding to the lower lobe, the percussion note is markedly impaired, extending up as high as the spine of the scapula. Over the lower axillary and subscapular regions, the breath sounds are enfeebled. A scratching friction rub is just audible. In the apex of the axilla and at the angle of the scapula, the breath sounds have a slight tubular modification. The left lung is clear. No impression recorded.

On November 13, 27 days after operation, the patient was transferred to the medical service. Her wound was well healed; she still had pain and physical signs in the thorax. Temperature 100° F.

On the medical service, a diagnosis of pleurisy with effusion was made. The temperature remained below 100° F. An order was left for her discharge three days after her transfer to the medical department. In preparation for her departure, she was up and dressed at 7 a. m., when she had a sudden collapse and died. Following is the note of the intern: "November 17, 1900. Last night the patient said she was feeling better than at any time since operation. She slept soundly. At 5 a. m. she said she felt perfectly well. She had been discharged the night before and was to leave on the 9 a. m. train. She dressed at 7 o'clock and felt well. A good breakfast at 7.15. She complained of pain around the heart, and a few minutes later said she felt faint. She was put in a chair and laid down. The pulse stopped almost immediately.

We report this case in detail because it is interesting for several reasons:

First, the operation was clean and there was no wound infection; second, there was no evidence of phlebitis; third, it was undoubtedly a case of fatal pulmonary embolism that was preceded by infarction.

We have two such cases in our series, Nos. 8222 and 18,020. Both of these patients had pulmonary infarcts which were unrecognized although the clinical picture was typical. In both cases the patients left their beds while the temperature was still elevated, and in both cases died suddenly. Perhaps they might not have recovered in any event, but we feel that their chances would have been better had they been kept quiet. Our statistics show that all cases of phlebitis are treated carefully and kept in bed, although only 1.5 per cent of them develop embolism. Cases of pulmonary infarction show a mortality of 15 per cent, but do not have the precautions taken with them that they deserve, mainly because they are not diagnosed.

CASE 2.—*Gyn. No. 3492. Atypical pulmonary embolism with abdominal symptoms. Previous infarction. Embolism diagnosed intra-abdominal hæmorrhage. Exploratory laparotomy negative. Femoral thrombophlebitis. Recovery.*

A widow, aged 39. Six miscarriages. No children.

Complaint.—Tumor of abdomen.

General Condition.—Good, except for slight anæmia.

Diagnosis.—Myomata uteri, uncomplicated.

Operation.—May 11, 1893. Supra-vaginal hysteromyomectomy.

May 18. Sharp pain in left chest, worse on deep inspiration. Temperature 101° F. Friction rub over eighth rib anteriorly. No other positive signs.

Impression.—Dry pleurisy.

May 19. Still complains of pain in left chest. Temperature 102°. Pulse 104. Patient has short dry cough.

May 22. Temperature 101° F. Pulse 100. Patient better, has less pain. Straps removed. Friction rub heard. No effusion.

May 24. The signs of pleurisy have disappeared. Temperature 98.5° F. Pulse 80.

May 29. Since the time of the last note, the patient has been improving until this morning, when she was suddenly taken with a fainting spell while sitting upon the chamber. She was at once put to bed and her pulse noted. It was very weak and rapid, rate 120. As soon as the patient had recovered, she commenced to complain of a heavy sensation over the sternum. This increased until 4 o'clock; at this time a thorough examination of the chest disclosed nothing. Pulse 120, feeble and at times almost imperceptible. Strychnin given. At 6 o'clock the patient was seen again; pulse 128, not improved in volume.

Although the symptoms of hæmorrhage were marked, it was still felt that there might be some complications in the chest, but another thorough examination of the heart and lungs by the medical chief showed nothing. Preparations were at once made for an exploratory laparotomy. The possibility of a pulmonary embolus was suggested. The symptoms were: Dyspnœa, rapid feeble pulse, rate 140, cold and clammy extremities, action of heart irregular, dark spots in front of eyes, ringing in the ears and a heavy aching pain over the sternum.

The patient was taken to the operating room, anæsthetized with chloroform, and the abdomen quickly opened. The line of first incision was perfectly healed; the second incision was made to the left of the first one. When the peritoneal cavity was opened no trace of hæmorrhage was found and no adhesions: everything was apparently in perfect condition. The wound was closed with silkworm gut. The operator now believed the case to be one of pulmonary embolism.

May 31. Pain in the left leg along the femoral vein. Marked tenderness along course of both femoral and popliteal veins.

June 9. Right leg also swollen and œdematous below the knee, not so large, however, as was the left when at its maximum.

June 14. Cervical glands swollen and very painful.

June 16. Pain along course of brachial artery.

June 17. Arm still painful; glands of neck less swollen; right leg almost well.

June 29. Patient discharged. Temperature 99° F.

This case illustrates again the necessity of diagnosing pulmonary infarction. She had been submitted to the operation most frequently associated with phlebitis, infarction and embolism—hysteromyomectomy. After her post-operative rise had subsided, she ran a daily temperature of 100° F. On the eighth day she had her first infarction, the temperature reaching 103° F. on the following day. The infarction was diagnosed as dry pleurisy. After she had recovered from this so-called "dry pleurisy," she was allowed to get out of bed. On the 11th day following the first attack, after the symptoms had disappeared and the temperature had become normal, she had a second and larger embolus that almost proved fatal. It is rather remarkable that this patient survived an infarction, an embolism and two laparotomies, all in less than three weeks, the second laparotomy being performed during the acute collapse following the embolism. The association of infarction, embolism and phlebitis in one case is rather unusual. We make no apology for presenting the details of this case; she was seen by the chiefs of two departments and is an illuminating example of atypical symptoms in pulmonary embolism.

CASE 3.—*Gyn. No. 24894. Atypical pulmonary embolism with cerebral symptoms. Death. Autopsy 5920.*

The patient was a large negress, aged 45. She was admitted in the spring of 1919 and was in good physical condition with the exception of a rather high grade of arteriosclerosis and a blood-pressure of 204/120 (Tycos, ausc.). Temperature 98.6° F. Pulse 92. The urine contained a trace of albumin, but no casts. Because of her hypertension, she was given a period of rest in bed before operation. Her renal function, as measured by the phenolphthalein test and absence of œdema, was normal.

Diagnosis.—Umbilical hernia.

Operation.—Radical cure for umbilical hernia.

Convalescence.—Normal, except for a slight elevation of temperature and small serous collection in one angle of the wound. Temperature, 100° to 100.6° F. through convalescence. Temperature on the day before embolism, 100.2° F., pulse 92; on the day of embolism, 101° F., pulse 116; just before death, 102.4° F., pulse 108.

On the 12th day, while the patient was still in bed, she suddenly became dyspnœic, markedly cyanotic, with a pulse of 116, and passed into a semi-conscious state, making no complaints of pain or discomfort. When aroused, she answered questions intelligently by nods of the head or a few words, her speech being hesitating and difficult. She almost immediately would lapse back into unconsciousness, breathing rapidly and deeply. She showed marked hyperæsthesia, reacting to light touches by general trembling and at times almost mild convulsions of a general type. The left side of her face was slightly drawn, with marked twitching of the muscles of that side. There was no spasticity of the extremities or anisocoria as there was in case No. 7361. Blood-pressure, 145. Lungs clear on auscultation and percussion. By means of oxygen the respiratory rate was lessened and the pulse made slower. While the oxygen was being administered the patient would become very quiet and pass into a sound sleep, the cyanosis disappearing more or less. After the oxygen mask was removed, she would soon revert to her former condition. After 18 hours, she died.

Autopsy 5920.—Anatomical Diagnosis: Pulmonary embolism. Œdema of lungs. Arteriosclerosis. Infarct of spleen. Bilateral fibrinous pleurisy. Myoma of uterus, small.

The operative incision had healed *per primam*, except for a small collection of fluid in the fat.

Heart: The pericardium contains 100 c. c. of clear fluid; except for few old adhesions it is negative. Heart hypertrophied, weighing 540 grams. Endocardium smooth, valves clear. Muscle negative. Right ventricle contains a small true venous thrombus.

Lungs: A large number of small emboli in pulmonary arteries of both sides. Lungs everywhere crepitant, air containing, no areas of consolidation. No bronchopneumonia.

Brain: Negative.

Source of embolus: Not determined.

CASE 4.—*Gyn. No. 13296. Simple pulmonary infarction. Recovery.*

A colored woman, aged 38 years, admitted to The Johns Hopkins Hospital, November 9, 1906.

Complaint.—Tumor of lower abdomen, first noticed 13 months before admission. General condition excellent. Well nourished. Temperature 98.6° F. Pulse 80. Lower abdomen and pelvis filled with a fibroid arising from the fundus of the uterus.

Operation.—October 10, 1906. Hysteromyomectomy, double salpingo-oöphorectomy. No unusual complications.

Post-Operative Convalescence.—After the first week, the patient settled down for a normal convalescence, on full diet, the bowels moving regularly, with no complaints and no pain. Temperature on the seventh day, 100.2° F. Pulse 118.

October 20. Wound dressed, healed *per primam*, clean. Abdomen everywhere soft. General condition excellent. Temperature still rising to 100° or 101° F. every afternoon, pulse 90 to 100. No reason for fever found.

October 24. Patient up in chair to-day for first time. Convalescence still uninterrupted, except for slight elevation of temperature, 99.6° to 100° F. to-day.

October 26. The patient to-day complains of sharp pain in the left side of the chest, near the base, also anteriorly over the lower part of the sternum. Breathing difficult, the patient being forced to take numerous short breaths because of pain. Examination of chest showed upper fronts and backs apparently clear. Suggestive dulness at bases on both sides in backs, not definite. No râles, no friction rub. W. B. C. 21,800. Temperature 100.4° F. Pulse 108. (See temperature chart, Fig. 3, page 103.)

October 28. Patient no better this morning. Dyspnœa. Severe pain on inspiration. Temperature 102° F. Pulse 124. Respiration 48 to 58. During the last 24 hours the patient has been expectorating a frothy, slightly tenacious, mucoid, blood-stained sputum, about 1½ ounces in 24 hours. Examination of chest shows definite dulness in lower back on left side, with tubular breathing over a small area. Friction rub not definitely heard. Abdomen soft, No tenderness. Wound healed. Morphin has been necessary during the past 48 hours. W. B. C. 16,8000.

October 30. Patient much better to-day. Slight dyspnœa, but still expectorating very small amounts of bright red, blood-stained, frothy sputum, about half an ounce in 24 hours. Temperature 100.4° F. Pulse 102. Respiration 24 to 30.

October 31. Condition about the same. Patient says that constant cold applications to the left back and over the heart make pain less. Takes liquid nourishment well. Very little sputum. Examination of sputum for tubercle bacilli, negative. Temperature 99.6° F. Pulse 96. Respiration 24 to 32.

November 1. Patient had a very good night. Temperature not above 98.6° F. since 8 a. m. to-day, pulse 80 to 86, respirations 24 to 28. Has no pain in side, except on taking a deep inspiration or moving about. Examination of left chest shows dulness of percussion note at base with tubular modification of breath sounds. Morphin discontinued. Sputum negative for tubercle bacilli.

November 2. General condition improving. Patient comfortable. Temperature 99.2° F. Pulse 92. Respirations 24.

November 3. Patient doing very nicely. W. B. C. 10,000. Sputum negative for tubercle bacilli.

DISCUSSION

These notes are extracted practically verbatim with some abbreviations from the history of this patient. Her further course was uninterrupted. She had an occasional slight pain in the left side of her chest for a week or more after the last note made above. Her sputum and cough disappeared entirely. There was some impairment of the percussion note and the breath sounds were slightly roughened until the end of the third week after the infarction, showing the time necessary for complete resolution. There was also a slight elevation of the temperature at times, running up to 99.4° or even 100° F. occasionally. On the 19th day after her infarction she was allowed to be up in a chair for the first time and was discharged on the 25th day. She had no pain or swelling of the legs at any time. The temperature chart of this patient during the acute symptoms of the infarction is found earlier in the article (page 103) showing the difference between it and a typical post-operative bronchopneumonia.

CASE 5.—*Gyn. No. 12587.. Pulmonary infarction, multiple abscess formation. Death. Autopsy 2651.*

Patient, a rather sick colored woman, aged 39. Admitted to hospital December 30, 1905.

Complaint.—Tumor in the abdomen, nausea and vomiting. Married seven years, no pregnancies. Abdomen irregularly enlarged by a hard nodular mass rising from pelvis to level of umbicilicus. Slightly tender over McBurney's point. Pelvis choked by this large tumor. Lungs clear on auscultation and percussion.

Diagnosis.—Myomata uteri.

Temperature 97° to 98.5° F. Pulse 100. Respirations 24. Hb. 70 per cent. Urine contains a few coarse and finely granular casts, with a trace of albumin.

Operation.—January 3, 1905. Hysteromyomectomy. Double salpingo-oöphorectomy.

Tumor very vascular, bound down by many vascular adhesions. Pulse during operation 140 to 150. Ether well taken.

Post-operative Notes on Convalescence.—January 4. Patient left operating table yesterday in rather poor condition. Pulse 148. Temperature normal. Respiration 26. Not much nausea or vomiting. Received subcutaneous salt infusion on operating table. During afternoon, pulse became weaker and more rapid, requiring stimulation with digitalis, strychnin and proctoclysis. Pulse to-day stronger and slower, rate 128, respiration 28, temperature 98.4°, rising to 99.8° F. in the afternoon. Taking fluids well. Conditions improving.

January 5. Patient's condition has improved markedly, pulse slower and stronger, rate 120. Strychnin discontinued. Bowels moved by enema. Has voided. Temperature 100° F. Respirations 24.

January 6. Last night at midnight patient complained of pain in her left chest. No cough. Temperature at that time 100° F., pulse rose to 136, respirations to 32. About an hour later she began to develop a slight cough, apparently dry and unproductive. By noon to-day, the temperature was 102.6° F. Pulse 160. Respirations 32. W. B. C. 30,600. On examination at 2.30 p. m. the patient looked ill. Pulse small and running. Slight dilatation of alæ nasi. Sordes on lips. No evident cyanosis. Chest: Right front and axilla clear on percussion. Occasional fine râle in lower axilla. Left side: marked tympany over and above clavicle merging with cardiac dulness. Also tympany at apex of left axilla. Elsewhere resonant. On auscultation, definite tubular breathing over left upper front. Breath sounds rather harsh at apex of axilla. Everywhere numerous rather coarse moist râles on inspiration and expiration. Just at anterior axillary fold a to-and-fro pleural friction rub can be heard.

On the left side behind, there is dulness over the upper portion from apex to midscapula. The note is nowhere flat, but has a tympanitic quality. Numerous fine dry râles over left upper back. Breath sounds nowhere tubular or especially harsh. If anything, vocal fremitus and vocal resonance are diminished over impaired area.

The patient does not seem toxic. A rather severe grade of abdominal distension has developed. Given turpentine stupes and enemata for distension; stimulant, and heroin and codein for thoracic pain.

January 7. Towards evening yesterday, the patient grew worse. Pulse remained around 160 and of poor quality. She responded poorly to stimulation. By midnight her condition was alarming. Temperature 104.4° F. Pulse 160. Respirations 52, labored with an expiratory grunt. Coughing rather frequently without appar-

ently producing anything. (No hæmoptysis noted.) Abdominal distension severe and intractable.

Physical signs unchanged in lungs. Given salt solution by hypodermoclysis, rather active stimulation and morphin. Patient seemed to respond well. The physician felt justified in leaving the ward. Fifteen minutes later, however, her respiration suddenly became more labored and gasping, her pulse practically imperceptible. Emergency measures were instituted without avail. She died at 5.25 a. m.

Autopsy 2651.—Anatomical Diagnosis: Operative wound, midline (hysterectomy for myoma) drainage wound in vagina. Acute fibrinous pelvic peritonitis. Thrombosis of uterine and vesicle veins. Embolism of pulmonary arteries. Lung abscesses and broncho-pneumonia. Acute bronchiectasis and bronchitis. Acute fibrinous pleurisy. Acute diphtheritic colitis. Cloudy swelling of the viscera.

Lungs: The left lung shows some fresh tags of fibrin over the anterior portion of the upper lobe. It shows a raised, firm area, quite airless, measuring roughly 5 cm. in diameter. Below this is a collapsed purplish area close to the margin of the lung, of doughy consistency. The lymph nodes are large and deeply pigmented, but show no caseous foci. The pulmonary arteries are clear at the hilum, but the smaller branches show numerous plugs loosely adherent to their walls, some of which can be removed easily, others with considerable difficulty. Some of the adherent ones are long and are like angleworms in appearance, resembling exactly the plugs found in the vesicle veins. The pulmonary vein is clear.

The larger bronchi show intense injection and purplish puffy mucosa. The smaller bronchi leading to the collapsed portion in the upper lobe are diffusely dilated along their course, out to within 0.5 cm. of the pleural surface, and contain a purulent material. Their walls are intensely injected.

The cut surface shows the large area of consolidation mentioned before to be airless and granular, of a grayish color, showing here and there softened areas up to 0.5 cm. in diameter, with an injected zone and a soft grayish center. The vessels here all show their lumina closed by ante-mortem clots. Most of the lung tissue is of a moist pinkish-red color and air-containing, dotted over thickly by these areas of consolidation with a zone of intense injection and central softening. The lower lobe shows a less extensive change, is voluminous, but shows here and there a small abscess.

The right lung is voluminous. Its artery shows many plugs of ante-mortem type. There appears to be no definite area of consolidation, except in the upper lobe, where there is a small area the size of a pea whose center is beginning to soften. The rest of the lung tissue is moist and deep red in color. The bronchi show intense injection throughout.

Microscopical Examination: The vessels show numerous emboli made up of fibrin, red and white blood cells. Some of these emboli show many fibroblasts at their margin and were evidently beginning to organize in the vessels where they were formed. There are many smaller and larger abscesses with complete softening of the lung framework. Some of the alveoli are packed with leucocytes and there is very little fibrin to be seen anywhere. In other places the alveoli contain much serous fluid and only an occasional cell. The bronchi, as a rule, show considerable injection,their lumina being full of leucocytes. There are some areas where there has been necrosis of lung tissue around large clumps of bacteria.

Pelvic Organs: The stump of the cervix is very much injected and closed in by catgut sutures. Some of the large veins on both sides of the cervix are tied by catgut ligatures and are thrombosed. From these veins there is an extension of the thrombosis to the much dilated veins around the base of the bladder. These vessels contain organized branched thrombi which are easily withdrawn from the lumina of the vessels.

Heart: Valves normal. Muscle normal in appearance. Microscopically normal.

DISCUSSION

We present this case to illustrate two main points: (1) The clinical history; and (2) the short course, due to severe complications.

1. The clinical history reveals a typical picture of pulmonary infarction, with one exception. It occurred on the fourth day of convalescence. This is rather early, as most of our cases occurred during the second or third week. Again, this patient had no hæmoptysis. To many of us, the presence of hæmoptysis has always been the cornerstone on which the diagnosis of pulmonary infarction rests. Our statistics show that just about one-third of our patients had hæmorrhagic sputum. In this case there was no pain or swelling of the leg. The thrombosis was entirely limited to the pelvic veins.

2. The short course that this case ran before death is rather unusual for pulmonary infarction. The onset was not very severe, there was no marked collapse, no cyanosis at the beginning. The patient apparently had many repeated small infarctions during the short period she lived. Autopsy showed that there were no large embolic masses, none of sufficient size to occlude a large vessel in the pulmonary system.

It seems that her rather sudden death was due to four factors complicating the infarctions. The poor condition of the patient before operation; a serious grade of operative surgical shock from which she was just beginning to recover; abdominal distension attending the pulmonary condition; severe infection of the infarcts. The poor condition of the patient before operation made her an easy prey to complications. She was just recovering nicely from the shock of the operation when the first infarction occurred. Abdominal distension almost immediately reappeared and became marked and uncontrollable. We have already called attention to the occurrence of abdominal symptoms in connection with embolism and infarction.

When to all these unfavorable factors was added the development of abscesses in the infarcts, the combination was fatal and the end came soon. Here again it is impossible to say whether the emboli were primarily septic in type, or whether they were bland and the infarcts merely furnished a good culture medium for the growth of organisms already present in the lung. It is probably true that early in convalescence the lungs are not as resistant to infection as they are after the congestion and irritation of the ether have worn off. In this connection it is instructive to note that half of our patients with infarction that died of either lung abscess or gangrene developed their infarctions during the first six days of convalescence.

CASE 6.—*Gyn. No. 17670. Pulmonary Infarction, followed by pulmonary gangrene. Death. Autopsy 3585.*

Patient a well-nourished negress, aged 24. Had had two children. Admitted to hospital, July 26, 1911. Operated upon July 29, and died August 14, 1911. General condition excellent. Temperature 99.2° F. Pulse 80. Urine negative.

Complaint.—Pain in abdomen. Profuse and irregular menses.
Diagnosis.—Chronic appendicitis. Metrorrhagia.
Operation.—July 29. Appendectomy. Dilatation of uterus and curettage. No unusual findings at operation. Appendix very adherent. Pelvic organs normal, except for slight enlargement of the uterus. Endometrium normal. Condition of patient at end of operation good.
Convalescence.—July 30 convalescence good. Slight distension, relieved by rectal tube. Temperature 100.8° F. Pulse 120.
July 31. General improvement. Liquid diet. Temperature 99.8° F. Pulse 116. Urine examination essentially negative.
August 1. Patient comfortable. No untoward symptoms. Bowels moved. Has been voiding well. Temperature still remains, however, between 99.5° F. and 100° F. Pulse 110.
August 2. First dressing. Wound clean, stitches removed. Complains of pain in left hypochondrium. Temperature 99.6° F. Pulse 110. Respiration 24. Physical signs negative.
August 3. Patient is having severe pain in left lower axilla, radiating through to left back. Pain is knife-like, worse on sudden or deep inspiration. Respiration shallow, rapid, restricted slightly over lower left thorax. Considerable dilatation of alæ nasi. Pulse rapid, full, bounding, 130 to minute. No cough. On examination of chest, percussion note seems unimpaired over both sides of chest. Vocal fremitus apparently increased in lower left axilla. Breath sounds suppressed in lower left axilla and below angle of left scapula. No tubular breathing, no râles heard, no friction rub. Temperature 101° F. Pulse 128. Respirations 38 to 42. W. B. C. 18,000.
August 4. To-day for first time the patient has been coughing, with occasional scanty expectorations of blood-streaked sputum. Cough is dry, harsh and painful. Over the left base there is slight impairment of the percussion note and at the end of inspiration many clicking râles can be heard. Expiration is harsh but not much prolonged. W. B. C. 24,000. Temperature 101.6° F. Pulse 120. Respiration 28 to 36. Sputum negative for tubercle bacilli.
August 6. Temperature 103° F. Pulse 120. Respiration 32 to 40. Profuse bloody expectoration. Quite marked cyanosis and respiratory distress. Percussion note is slightly dulled over upper left front, definitely flat over lower front, axilla and left back, below the angle of the scapula. Breath sounds are very harsh and accompanied by many sonorous râles, chiefly expiratory in time. There is a small area of tubular breathing, about the size of a silver dollar, in the back at the angle of the scapula. Below the breath sounds are very distant and transmission of the voice sounds is diminished. Heart, as before, not much dilated. Pulmonic second sound of good quality. Sputum negative for tubercle bacilli.
August 7-8. Temperature 103.4° F. Pulse 136. Respirations 42. Condition about same, except that at times she is more comfortable. Cyanosis and dyspnœa still marked. Physical signs about the same. Sputum contains no tubercle bacilli, but many chains of cocci and diplococci.
August 10. Condition much improved. Temperature lower, 101.4° F. Pulse still rapid, 140 to 150. Respirations 32 to 42. Patient comfortable. Dyspnœa still marked. Pulse strong and regular, though rapid. Profuse bloody expectoration continues. Examination of sputum reveals no tubercle bacilli, no elastic tisue. Physical signs essentially unchanged.
August 11. Temperature less elevated. Pulse continues rapid, is irregular. Respirations 40. Marked cyanosis at times with great respiratory distress. General condition, however, seems improved. Physical signs about the same—dulness over left front, flatness in left axilla and lower left back. Breath sounds harsh, accompanied by many dry and bubbling râles. Small area of tubular breathing at angle of scapula. Breath sounds and transmitted voice sounds are diminished or almost absent in left axilla. Vocal fremitus also absent over this area. Profuse bloody expectoration, rather frothy. No odor. Temperature 102° F. Pulse 130 to 155. Respiration 40.
August 13. Condition yesterday and to-day shows no improvement. This afternoon a peculiar nauseating sweetish odor was observed on the patient's breath and from the sputum. No gross masses in sputum, which is dark bloody. This evening, the temperature, which had fallen during the day to 99.8° F., rose a degree, the pulse became very rapid, 160 to the minute, weak, irregular, and finally could barely be felt at the wrist. Respiratory distress marked, rate 40, shallow, with expiratory grunt or groan, and marked cyanosis. On the left side of thorax there is marked restriction of respiratory movements, the lower ribs being held practically immobile. Vocal fremitus absent over lower axilla and back. Marked pulsation synchronous with heart beat, extending far out into the left axilla almost to the angle of the scapula behind. Other physical signs essentially the same.
An exploratory puncture with a fine needle was performed in the eighth interspace below the level of the scapula; pure dark blood was obtained. A thoracentesis was then done, and 200 c. c. of dark bloody fluid were obtained.
There is considerable abdominal distension.
August 14. The patient died to-day.
Autopsy 3585.—Anatomical Diagnosis: Operation, appendectomy, dilatation and curettage of the uterus. Bronchopneumonia, bilateral. Gangrene of base of left lung with cavity formation and terminal hæmorrhage. Acute hæmorrhagic pericarditis. Acute fibrinous pleuritis. Acute fibrinous perisplenitis.
Thorax: When the thorax is opened the left pleural cavity is found to be obliterated by fine fibrinous adhesions. The apex is free. On separating these adhesions a large hole containing about two liters of dark blood-stained fluid is found in the base of the lung. This blood-stained fluid has a very offensive odor. On opening the pericardial sac, a small excess of blood-stained fluid is found and a hæmorrhagic exudate is found over the region of the left ventricle.
Heart: Normal size, 240 grams, epicardial surfaces everywhere normal. Right auricle filled with fluid blood. Surface smooth. Valves delicate, smooth. Right ventricle normal. Pulmonary valves delicate. Root of pulmonary artery normal. Left ventricle moderately filled with fluid blood. Endocardium smooth. Valves delicate, smooth. Aorta smooth, elastic. Heart muscle normal.
Lungs: Base of left lung is occupied by a large, ragged, worm-eaten cavity containing the above mentioned fluid. There are shreds and tags of tissue running through the cavity. On removal of the lung, the gangrenous area described measures 12 cm. in diameter. No lesion of the arteries is to be made out in gross, except at the apex. The lung is plastered over with a rather thick, fibrinous pinkish-colored exudate. This is rather easily torn away. The lobes are glued together. The lung is kept intact for injection of the blood-vessels.
On injection of the arteries after ligating the veins, there is found to be a general oozing as from a sieve. No definite rupture of an artery or vessel could be demonstrated. On section, the upper lobe is pale, pink in color, moist and everywhere crepitant. The lower lobe, on section, is firm, moist, of a rather dark grayish-red color, shading off at the base into gangrenous shreds and tags composing the wall of the cavity described. One small artery is found to contain a fresh thrombus. The other vessels are negative. The structures at the hilum are normal, except for slightly enlarged pigmented glands.
The right lung is fairly voluminous, of a pale gray color, mottled with hard, raised, pinkish-brown areas. The structures at the hilum appear quite normal except for the glands which are slightly enlarged and of a gray color mottled with black coal pigment. The upper lobe on section is pinkish-gray color, rather moist, and everywhere crepitant. The middle lobe is crepitant only in

small areas. The rest of the lobe is voluminous, nodular, firm, very moist and of a pinkish-gray color. The cut surface shows irregular raised areas which are firm, not containing air. The lower lobe likewise feels nodular and shows a few dark areas projecting upon the surface. On section, the lung shows irregular raised nodules of darker red lung tissue, not containing air. No abscesses are found throughout the lung.

Origin of Thrombi: The pelvic veins show no thrombus masses.

Culture of Thrombus or Abscess: Not reported.

DISCUSSION

This case is presented in detail for three reasons:

(1) It gives the clinical and pathological picture of a type of pulmonary infarct with a very serious complication—infection. Whether the abscess formation and gangrene came as the result of an infected embolus or whether they were due to a bland embolus lodging in an infected lung, is sometimes a difficult and usually a purely academic question. In this case, the absence of pulmonary symptoms and signs before the infarction, and the occurrence of the infarction on the fifth or sixth day might lead one to believe that the infection was transported to the lung with the embolic material. On the other hand, a patient who has had an ether anæsthetic and has been in bed continuously for a week might very well have a certain amount of hypostatic congestion of the lower lobes of the lungs and an inactive low-grade bronchitis. Given such conditions as this, the addition of a good culture medium like a fresh infarct makes the opportunity for activation of the infection favorable indeed.

(2) This case shows, moreover, the difficulty of establishing a clinical diagnosis unless the history of onset is considered. After development of the abscess and gangrene, the clinical picture of infarction is wholly lost. The infected lung is drained by its bronchus; and the aspiration of the infected material from this lobe into others soon gives rise to patches of bronchopneumonia which complicate the original picture.

(3) The difficulty attending the diagnosis of pulmonary embolism and infarction on the autopsy table is also brought out by this post-mortem examination. Emboli are frequently not fixed; they are often loose in the pulmonary artery. Hence they must be searched for *in situ* before the organs are removed. After a certain length of time, emboli may become liquefied. This applies particularly to small particles such as would cause infarcts. Infection would also tend to hasten liquefaction. In this case in particular, while only one small thrombus was found, the pathologists expressed the opinion that the cause of the pulmonary complication was undoubtedly infarction.

NOTE.—We wish to express our indebtedness and thanks to Dr. Howard A. Kelly and Dr. Thomas S. Cullen for their kindness and suggestions to us in the preparation of this paper. The medical department, also, has always shown us the greatest courtesy in giving us the benefit of consultation. This has been utilized in practically all the pulmonary cases. To the department of pathology we are indebted for free access to the records of all our cases that were examined at autopsy.

For the benefit of any who might in the future care to examine this subject in greater detail, we shall herewith give the list of the cases on the basis of which this report has been made. The 34 cases which we have diagnosed pulmonary infarction are as follows, the designations referring to the gynæcological numbers in the Johns Hopkins Hospital: 8222, 4902, 3492, 4955, 6659, 660, 7534, 7996, 10653, 11060, 13908, 13354, 17253, 16960, 18375, 8764, 10204, 10569, 12287, 12663, 16250, 13296, 14369, 19697, 21083, 1004, 13340, 17670, 1576, 19810, 21562, 12587, 20338, 24747. Of these 34 patients, the following died: 8222 (autopsy refused); 1004 (autopsy No. 304); 12587 (autopsy No. 2651); 13340 (autopsy No. 2801); 17670 (autopsy No. 3585).

The cases of fatal pulmonary embolism which we have included are as follows:

Gynæcological number	Autopsy number
24894	5920
20709	4223
21375	4413
22338	4790
76	54
2492	486
6939	1374
24747	5869
7361	1445
8713	1733
16840	refused.
17503	3553
18020	3659
19872	4037
19006	3864
23670	5432
25390	refused.
8222	refused.
13340	2801

There were four cases of pulmonary embolism with previous pulmonary infarction, Gyn. Nos. 8222, 13340, 3492, 7996. Of these, the first two resulted fatally and are included in the above list.

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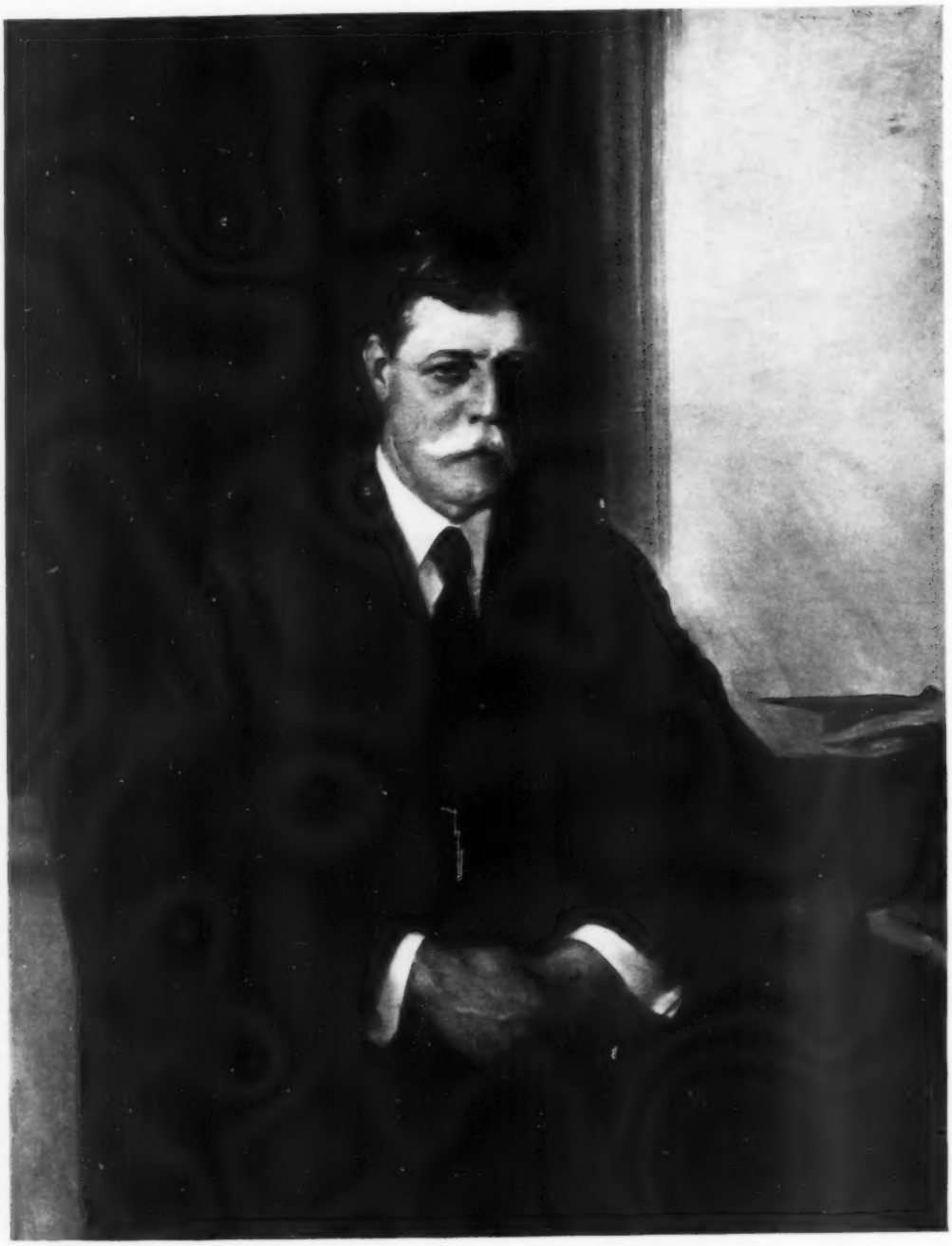

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PRESENTATION TO THE UNIVERSITY OF THE PORTRAIT OF DR. JOHN WHITRIDGE WILLIAMS

Mr. President, Members of the Board of Trustees, of the Faculty, and Alumni of the University, Ladies and Gentlemen:

In behalf of the donors I have been requested to present to you the portrait of Dr. John Whitridge Williams. The donors of this portrait are the graduates of the medical department of the university. Already no less than two-thirds of these graduates have subscribed, their subscriptions being accompanied with warm expressions of appreciation of the services of Dr. Williams—a remarkable tribute to him I venture to say.

The painter of this portrait is Mr. Wayman Adams, a young artist of Philadelphia, whose work is already most favorably known, an artist of established and increasing reputation.

Dr. Williams was graduated in arts from this university in 1886 and in medicine from the University of Maryland in 1888, just one year before the Johns Hopkins Hospital was opened. After a short period of foreign study he became connected with the hospital first as an assistant to Dr. Kelly in the department of gynecology, and later on the obstetrical service of the hospital, of which he was placed in charge and has remained in that capacity until this time. The entire organization and development of the department of obstetrics both in the hospital and in the medical school is his work. It is not a little remarkable, I think, inasmuch as the Johns Hopkins Hospital was designed from the beginning to serve the needs of the medical school as a teaching hospital, that no provision was made for the care of obstetrical patients. It is only now that a new building, the funds for which are contributed by an anonymous and most generous donor, is to be erected to provide for the obstetrical department. Dr. Williams has developed his service and his teaching under not inconsiderable difficulties and obstacles. Therefore, the results which he has obtained are the more creditable to him, and to the medical school; and I may say too that the contributions which he has made to his subject are the more remarkable in view of the handicap under which he has worked.

Dr. Williams was born and bred in Baltimore—a member of a family well known in the social and professional circles of this city. Where so many of us were imported from the outside it is no small satisfaction that we found here one who has served the university so faithfully and brought such distinction to the hospital and to the university.

An admirable teacher—an important contributor to his subject! This is not the occasion to indicate the value and extent of these contributions. It must suffice to say that they are recognized the world over—his text-book, the recognized one in this country, is used to no small extent on the other side of the water.

He has been an important influence in the medical department. Always a sympathetic friend to the students of the university, it is not surprising that they should have been so ready to contribute toward the perpetuation of his memory in this portrait. It is fitting, I think, that the portrait should be presented at this time, when the difficulties under which the department of obstetrics has labored are about to be, to a large extent, removed, when after these many years of effort

and struggle the department is placed upon a secure and admirable basis. Himself an advocate of what we call the university full-time system of teaching in our medical school, —Dr. Williams' department will now be reorganized on the full-time basis, the funds for which are generously donated from the same source from which the original endowment came, the General Education Board.

It is a special privilege for me, and I am sure it is a source of great satisfaction to all of his colleagues in the medical faculty, and in the university, to be able to present this portrait of one who, in his later years as dean of the medical department of the university has contributed so loyally, so devotedly, so unselfishly of his time and work to the university. An admirable teacher, a loyal supporter of the best academic ideals, a friend of the students and of the alumni, a real ornament to the university, Dr. John Whitridge Williams.

NOTE.—Stenographic notes of remarks made at the Commemoration Day Exercises, February 23, 1920, by Dr. William H. Welch, but not revised by speaker.

THE FATE OF BACTERIA INTRODUCED INTO THE UPPER AIR PASSAGES

IV. THE REACTION OF THE SALIVA

By ARTHUR L. BLOOMFIELD and JOHN G. HUCK

(From the Biological Division of the Medical Clinic, The Johns Hopkins University and Hospital)

One of the most important phases of recent work in bacteriology has been the attempt to study and define more clearly the exact conditions underlying the growth of microorganisms. Whereas in the early years of microbiological study such conditions were for the most part regarded as being relatively crude, it is now known that in the case of many pathogenic bacteria a subtle combination of circumstances is essential not only for optimal growth, but even for the initiation of any growth. Failure of some workers to isolate influenza bacilli during the recent epidemic was clearly due to the faulty methods, because very slight variations in the composition of the media may make all efforts unsuccessful, and similar precautions are necessary in growing in the most advantageous manner the pneumococcus, meningococcus, gonococcus and other organisms.

Of the many qualities which are essential to a favorable environment for bacterial growth one of the most important is the proper hydrogen-ion concentration of the medium. Much work has now been done which shows conclusively not only that growth ceases when the reaction of the medium passes beyond certain limits, but also that a definite pH is necessary for the initiation of growth. Clark and Lubs [1] review the literature on this subject up to 1917 and point out its bearings in connection with the growth of the members of the typhoid-colon group, streptococci, yeasts and moulds. Avery [2] recently has studied in detail the reaction limiting the growth of streptococci and pneumococci. He emphasizes the importance of distinguishing between the final hydrogen-ion concentration, that is, the point at which growth stops in the culture—and the limiting reaction or pH above which growth cannot be initiated. In the case of the pneumococcus for example, it was found that growth once initiated continued until a reaction of pH 5.0 had been reached, but that growth could not be started in the same medium if its reaction were more acid than pH 7.0. The exact manner in which the multiplication of bacteria is influenced by the pH of the environment is uncertain, but observations on the relation of acidity to enzyme action and on the physical condition of colloids (see Clark and Lubs) are suggestive.

In studying the fate of organisms introduced into the upper air passages [3] it was found that certain bacteria disappeared very rapidly, the explanation apparently being that conditions were relatively unfavorable for growth and that the organisms were therefore washed away more rapidly than they multiplied. It seemed possible that the reaction of the saliva might be of importance in favoring or inhibiting bacterial growth. The following observations were therefore collected as a preliminary to test-tube experiments on the effect of saliva of various reactions on the growth of bacteria:

THE MOUTH AND NASAL SECRETIONS

Without attempting to enter into in detail the physiology and chemistry of the mouth and nasal secretions a few points of importance in the present connection may be recalled. The saliva as found in the mouth is a mixed secretion derived from the salivary glands and from the small glands situated in the lips, palate, tongue, sublingual space, and pharynx. To this may be added the nasal secretions which drain back into the pharynx through the posterior nares. This composite secretion is both serous and mucous and varies constantly and is influenced by a variety of conditions, at times being a profuse colorless or opalescent thin fluid and again a more viscid, thick material. The acts of swallowing and expectoration in conjunction with the stimuli of food, drink and irritants, lead to a constant production and flux of these mouth fluids. Among the important constituents of the saliva may be mentioned ferments such as ptyalin and maltase, traces of protein, mucin, and inorganic salts—chlorides, phosphates, carbonates, and sulphates. The carbonates are very abundant and may be important in connection with the reaction of the saliva.

There is also much CO_2 in solution. Potassium sulphocyanid present in small amounts has been thought by some writers to have an antibacterial action. The reaction is weakly alkaline to litmus.

We have been unable to find in the literature any detailed study of the reaction of the mouth secretions under various conditions. Michaelis and Pechstein [4] in another connection report a few observations. Six specimens of saliva were found to have a pH respectively of 6.79, 6.91, 6.92, 6.65, 6.34, and 7.01. The first three observations were made on undiluted saliva, the last three on saliva diluted one to ten with water. The tests were made by the electrometric method.

METHODS

The individual to be examined was requested to gather a mouthful of saliva. By churning the secretion in the mouth a composite mixture was obtained. This was expectorated into a graduate and immediately centrifuged at high speed for five minutes to throw down gross particles. The clear supernatant fluid was then decanted. One cubic centimeter of this was measured into a standard test-tube and 9 c. c. of freshly distilled water were added. The proper amount of indicator was introduced, the contents of the tube mixed by rotation and the reading made by comparison with a set of standard tubes of different pH. The indicators used were phenolsulphonphthalein and alizarin, covering respectively the range from pH 8.3 to pH 6.6 and pH 6.6 to pH 5.0. Four drops of .04 per cent solution of phenolsulphonephthalein and one drop of .2 per cent alizarin to 10 c. c. of the standard and of the test mixture were found to give the best color differentiation in this work. The test mixtures with this technique gave a clear limpid fluid which could be readily and accurately compared with the standard tubes. The readings were always made within 15 minutes of the collection of the specimen.

TECHNICAL CONSIDERATIONS

1. *Glassware.*—The same set of glassware—test-tubes, centrifuge tubes, pipettes, and graduates was used throughout the work. It came in contact with no alkali, acid, or strong chemicals which might have influenced the readings. Immediately before use it was thoroughly rinsed with freshly distilled water.

2. *Water.*—Freshly distilled water was used in all the tests for diluting the saliva. Its pH was usually 6.0 to 6.2.

3. *The Standard Solutions.*—The standard solutions were freshly prepared every two weeks from buffer mixtures supplied by the chemical laboratory of the medical clinic.

The technique was furthermore checked in various ways.

4. *The Effect on the pH of the Saliva of Contact with Air.*—Inasmuch as the saliva contains a considerable amount of CO_2 it was necessary to determine the alteration in reaction resulting from the specimen standing in contact with the air. Specimens were collected and one part was immediately covered with paraffin oil. The remainder was placed in a tube in contact with the air. The pH of both specimens was determined after various intervals (Table I).

TABLE I.—EFFECT OF CONTACT WITH AIR ON THE pH OF SALIVA

Specimen	pH immediately after collection	pH after standing in contact with air		pH after standing under paraffin oil	
		20 min.	60 min.	20 min.	60 min.
B	6.6	6.6	.....	6.6	.....
B	6.7	6.7	6.8	6.7	6.7
S	7.0	7.0	7.0+	7.0	7.0
D	6.2	6.2	6.3	6.2	6.2
B	6.9	6.9	7.1	6.9	6.9

These observations show that the pH of the saliva was not appreciably altered by twenty minutes contact with the air. In doing the tests readings were always made within this length of time from the collection of the specimen.

5. *The Buffer Value of the Saliva.*—To obtain clear suspensions of saliva it was found necessary to dilute the expectorated material with nine parts of water. Tests were made to determine if the saliva contained enough buffer salts to allow such a dilution. Distilled water containing the proper amount of indicator was added to the saliva until there was a noticeable change in color. The buffer value for 1 c. c. of various specimens of saliva in terms of distilled water is shown in Table II.

TABLE II.—BUFFER VALUE OF SALIVA

Specimen	pH	Buffer value for 1 c. c. in terms of distilled water	pH of water
B	7.1	22 c. c.	6.0
H	6.7	20 c. c.	6.0
M	7.4	20 c. c.	6.0
C	6.9	20 c. c.	6.2
B	6.9	16 c. c.	6.2
B	6.1	35 c. c.	5.6
L	6.4	25 c. c.	6.0
D	7.1	25 c. c.	6.2

It is apparent that the saliva contains enough buffer substances to allow a dilution of 1:10 without altering the reaction.

RESULTS

Normal Individuals.—One hundred and two observations were made on 52 clinically normal individuals during a period of about two months. The specimens were collected at various times during the day and at night without particular reference to the intake of food or fluid, smoking, or cleaning the mouth. It was desired to cover all possible normal variations in the condition of the mouth. As may be seen in Table III,

TABLE III.—REACTION OF SPECIMENS OF SALIVA FROM HEALTHY PEOPLE

	pH	6.0	6.1	6.2	6.3	6.4	6.5	6.6	6.7	6.8	6.9	7.0	7.1	7.2	7.3
Number of specimens.....	....	2	2	3	3	2	7	19	7	8	18	16	12	1	1

the reaction of 80 per cent of the specimens fell within the range of pH 6.6 to pH 7.1, although the limits for the whole group were pH 6.0 to pH 7.3.

A number of readings were made on saliva from the same persons at various times to determine whether the reaction was constant in any one individual and if not whether any regular variation occurred (Table IV).

TABLE IV.—VARIATIONS IN pH OF SALIVA IN THE SAME INDIVIDUAL

Name	Period of observation	pH														Total obs.
		6.0	6.1	6.2	6.3	6.4	6.5	6.6	6.7	6.8	6.9	7.0	7.1	7.2	7.3	
		Number of observations														
H.	2 months	2	1	..	1	..	2	6	2	1	4	..	..	..	..	19
Br.	2 days	..	..	..	..	..	..	..	..	1	..	1	..	..	..	2
Ko.	2 days	..	..	..	..	..	..	..	..	1	..	..	1	..	..	2
Sch.	1 day	..	..	..	..	..	..	..	..	..	1	1	..	..	..	2
B.	3 weeks	..	2	..	..	1	..	1	1	..	1	1	2	..	..	9
D.	1 week	..	..	1	..	..	..	..	..	..	..	1	..	..	..	2
N.	5 days	..	..	..	..	..	..	..	..	..	1	..	3	..	1	5
M.	5 days	..	..	..	..	..	..	1	..	1	2	..	1	..	..	5
Bl.	1 day	..	..	2	1	..	..	..	..	1	..	1	..	..	..	5

It was found that the variation in the individual covered practically the entire range of the normal reaction, although many of the repeated observations were made at the same time of day and under the same conditions. In a few cases several observations were made during the course of the day to see if there was any regular diurnal variation (Table V).

TABLE V.—DIURNAL VARIATION IN pH OF THE SALIVA

Name	Time	pH	Name	Time	pH
H.	9.15 A. M.	6.6	B.	9.00 A. M.	7.0
	11.45 A. M.	6.6		11.00 A. M.	7.3
	4.15 P. M.	6.6		4.00 P. M.	6.7
	7.30 P. M.	6.3		7.00 P. M.	6.9
In.	9.00 A. M.	6.6	Bl.	9.00 A. M.	6.2
	11.00 A. M.	6.6		1.00 P. M.	6.3
	4.00 P. M.	6.8		2.00 P. M.	7.0
	7.00 P. M.	6.6		3.00 P. M.	6.2
				5.00 P. M.	6.8

A few tests were made to determine the effect of food on the reaction, by examining the saliva immediately before and after meals (Table VI).

TABLE VI.—REACTION OF SALIVA BEFORE AND AFTER MEALS

Name	pH before meal	pH after meal	Name	pH before meal	pH after meal
S.	6.5	6.2	Ma.	6.4	7.3
H.	6.0	6.0	B.	6.5	6.6
M.	6.3	6.3	Bl.	6.2	7.0

No striking changes were noted. Smoking failed to alter the reaction.

Determinations were made to discover any possible alteration in the pH of the saliva following cleaning the mouth and irrigating with the usual gargles used in medical practice (Table VII).

TABLE VII.—EFFECT ON THE pH OF SALIVA OF IRRIGATION OF MOUTH

Name	Procedure	pH before irrigation	pH after irrigation
B.	Mouth washed with 500 c. c. distilled water.	6.9	6.9
L.	Mouth washed with 250 c. c. salt solution followed by 500 c. c. distilled water.	6.4	6.3
C.	Mouth washed with 1000 c. c. distilled water.	6.9	6.9
H.	Mouth washed with 1-1000 potassium permanganate.	6.1	(30 min.) 6.3
B.	Mouth washed with 1-1000 potassium permanganate.	6.6	" 6.6
I.	Mouth washed with 1-1000 potassium permanganate.	6.6	" 6.6
E.	Mouth washed with 1-1000 potassium permanganate.	6.6	" 6.7
H.	Mouth washed with potassium chlorate mouth wash.	6.5	(immediately) 6.7 (30 min.) 6.5
B.	Mouth washed with potassium chlorate mouth wash.	6.6	" 6.9 " 6.7
I.	Mouth washed with potassium chlorate mouth wash.	6.6	" 6.9 " 6.6
H.	Dobell's solution.....	6.5	" 8.3+ " 6.9
B.	" "	6.6	" 8.3+ " 6.7
I.	" "	6.6	" 8.3+ " 6.6

Washing with distilled water led to no change in reaction of the saliva, and gargling with Dobell's solution, potassium chlorate 25 per cent, and potassium permanganate 1-10000 caused only brief alterations which were no longer striking after 30 minutes.

The effect of internal administration of acid and alkali was tested as follows: A normal man received 10 gms. of sodium bicarbonate twice daily until the urine became strongly alkaline. The saliva was tested at various times, care being taken not to collect a specimen until at least two hours after the alkali had been ingested. A similar experiment was performed with hydrochloric acid (Table VIII).

TABLE VIII.—EFFECT OF ACID AND ALKALI ON THE pH OF SALIVA

Name	Date	pH of saliva	Remarks
M.	XII, 2, 19—11 A. M.	6.9	Urine acid.
	XII, 4, 19— 4 P. M.	6.8	Sodium bicarbonate grams 10 b. d.
	XII, 5, 19— 4 P. M.	6.8	
	XII, 6, 19— 2 P. M.	6.6	Urine alkaline.
	XII, 7, 19— 6 P. M.	7.1	
N.	XII, 2, 19—11 A. M.	7.3	
	XII, 4, 19— 4 P. M.	7.1	Dilute HCl 30 drops t. i. d.
	XII, 5, 19— 4 P. M.	6.9	
	XII, 6, 19— 2 P. M.	7.1	Urine acid.
	XII, 9, 19— 6 P. M.	7.1	

The change in the reaction of the urine was not paralleled by any alterations in the salivary reaction.

REACTION OF THE SALIVA IN DISEASE

Forty-eight observations were made on seventeen individuals suffering from various diseases (Table IX). The reaction

TABLE IX.—REACTION OF SALIVA IN DISEASE

Name	Diagnosis	Date	pH of saliva	Remarks
Br.	Typhoid fever.....	XI, 9, 19	7.0	Febrile.
		XI, 10, 19	6.8	"
K.	Typhoid fever.....	XI, 9, 19	7.1	"
		XI, 10, 19	6.8	"
C.	Typhoid fever.....	XI, 9, 19	6.9	Afebrile.
		XI, 10, 19	6.7	"
S.	Broncho-pneumonia.	XI, 7, 19	7.3	Temperature 101° F.
A.	Pernicious anæmia.	XI, 24, 19	6.0	
		XI, 25, 19	6.0	
		XI, 30, 19	6.3	
B.	Pernicious anæmia.	XI, 24, 19	6.1	
		XI, 25, 19	6.1	
T.	Syphilis of larynx...	XI, 8, 19	7.1	Scarring of pharynx.
		XI, 9, 19	6.9	
		XI, 10, 19	6.9	
Au.	Chronic nephritis (advanced.)	XI, 24, 19	7.5	Mouth and throat not remarkable. Not getting alkali. Urine acid.
		XI, 25, 19	7.5	
		XI, 26, 19	7.5	
		XI, 27, 19	7.3	
		XI, 28, 19	7.3	
		XI, 29, 19	7.3	
		XI, 30, 19	7.5	
P.	Chronic nephritis...	XII, 1, 19	7.5	
F.	Chronic nephritis...	XII, 1, 19	6.5	
A.	Chronic nephritis...	XII, 1, 19	6.0	On alkali therapy. Urine alkaline.
C.	Diabetes.....	XI, 28, 19	6.2	Acidosis. Blood CO_2 25 vols per cent. No alkali by mouth.
		XI, 29, 19	6.2	Intravenous alkali. Blood CO_2 35 vols per cent.
		XI, 30, 19	6.0	Intravenous alkali.
		XII, 2, 19	6.5	Blood CO_2 50 vols per cent.
		XII, 5, 19	6.9	
		XII, 6, 19	6.0	
		XII, 7, 19	6.9	Blood CO_2 75 vols per cent.
D.	Acute stomatitis....	XI, 7, 19	7.0	
K.	Acute tonsillitis (streptococcus).	XI, 8, 19	6.2	Throat acutely inflamed.
		XI, 10, 19	6.8	Throat clear.
W.	Acute tonsillitis (streptococcus).	XI, 14, 19	7.1	Throat acutely inflamed.
		XI, 15, 19	6.9	" " "
		XI, 17, 19	7.1	Throat clear.
		XI, 18, 19	7.0	" "
		XI, 19, 19	7.3	" "
		XI, 20, 19	6.9	" "
H.	Acute tonsillitis (streptococcus).	XI, 17, 19	7.1	Throat acutely inflamed.
		XI, 18, 19	6.9	
		XI, 19, 19	6.9	
		XI, 20, 19	6.9	Throat clear.
G.	Acute tonsillitis (streptococcus).	XI, 18, 19	5.8	Throat acutely inflamed.
		XI, 19, 19	6.5	
		XI, 20, 19	6.7	Throat clear.

of the salivas fell within the limits found for normals (pH 6.0 to pH 7.3) except in two cases, Au. and P. Three patients with typhoid fever showed a normal salivary reaction. In two instances of pernicious anæmia the reaction was at the lower level of normal on several occasions. Two cases of chronic nephritis had salivas which were distinctly more alkaline than any of the normals, but two other cases of nephritis gave high readings although one of them (A.) had an alkaline urine at the time. A series of five cases of acute streptococcus tonsillitis yielded variable readings within normal limits except for a single observation of 5.8. A diabetic with marked acidosis gave a reading of 6.2. A subsequent reading of 6.0 was obtained at a time when the acidosis had almost cleared up, although the reaction the day before had been 6.9.

SUMMARY

Study of freshly expectorated saliva from normal people shows that the reaction tested by the colorimetric comparison method may vary within considerable limits—6.0 to 7.3—although 80 per cent of the specimens fell within the range of 6.6 to 7.1. The reaction varied in different individuals and in the same individual at various times apparently without any definite or constant relation to the time of day or to the ingestion of food or fluid. It was temporarily altered by mouth-washes such as Dobell's solution, but only for a short time (30 minutes). Internal administration of acid and alkali did not seem to influence the reaction of the saliva in any definite manner. Observations on a group of patients suffering from a variety of diseases showed no constant relation between the reaction of the saliva and any particular disease, although the variations covered a slightly wider range (pH 5.8 to pH 7.5) than was found in the case of the normal group.

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SIR WILLIAM OSLER, Bart.

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PYELITIS ET URETERITIS ET CYSTITIS CYSTICA

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Cystic disease of the renal pelvis and ureter was first recognized by Morgagni, who, in *De Sedibus et Causis Morborum* described the autopsy findings in the bodies of two aged men. His Case IX, in Chapter IV, Section 1, was that of a man 60 years old, indigent, who died suddenly. There were found "hydatids in the substance of the kidneys and ureters, retention of urine from an enlarged prostate and serous infarction of the left thigh and knee. The interior structure of both kidneys contained some small cells full of fluid, one of which showed partly on the surface. Each pelvis was two digits in diameter, both ureters were dilated, the left more so than the right, the left elongated in consequence of flexures. On feeling the ureter there was a sensation of calculi in some portions. Slitting open the ureters disclosed hydatid cysts, some round, others oval, projecting from the inner coat into the canal of the ureter. The round cysts were of the size of small grapes, the oval double the length of the former. The coats of the ureter were thick, the inner uniformly reddened. The ureters opened into the bladder by orifices more oblong than normal. The bladder was distended with urine." In the section on gonorrhœa and syphilis, Case IV is that of a decrepit old man with lues, gonorrhœa and paresis. "The kidneys were small and uneven and the ureters dilated and with the inner surface reddened. In about the middle of the right ureter the inner coat protuberated and doubled itself. Both ureters were filled with mucus and from the middle upwards showed spherical drops of various sizes which could not be wiped away with a sponge. By compressing them they were reduced to a kind of viscid matter tinged with a very faint color of tobacco." The bladder was thickened and trabeculated and there was much pus in the urine.

Until 60 years later no new cases came to light. Johnson in 1816 reported the case of a female who after pregnancy had twice suffered with retention of urine. At autopsy one of the kidneys was found reduced to a shell by hydronephrosis and the ureter was dilated to the size of the iliac artery. The internal surface of the pelvis was highly vascular and studded with mammillary or papillary bodies varying in size from a pinhead to a pea. The cysts did not have the appearance of hydatids, nor were they strictly regarded as due to animal parasites.

These early observers have given us gross anatomical descriptions of a cystic condition of the lining of the pelvis and ureter and associated with it evidences of chronic inflammation in the kidney and ureter. The frequent occurrence of hydatid cysts in the kidney and other organs in Morgagni's experience naturally led him to consider the cysts in the ureter as probably hydatid. From his description of the kidneys the present-day pathologist would gather that the kidneys were probably of the small arteriosclerotic variety with many retention cysts. His cases were both in aged men. The importance of age in the development of the condition will be discussed later.

Litten, in 1876, made a careful study of a case and introduced the term "ureteritis chronica cystica polyposa." His patient was a man, aged 75 years, with small, shrunken kidneys and the right ureter dilated and studded with cysts. There was a calculus in the right ureter with hydronephrosis. Microscopically, the walls of the ureter were thin and highly vascularized. The cysts contained many free nuclei and masses resembling giant cells with irregularly distributed nuclei-like bodies.

Following Litten's contribution, over 50 cases of ureteritis cystica have gradually accumulated, the greater percentage from the experience of European pathologists, particularly the French and German, but the latter have given the most complete descriptions and have attempted to explain the pathogenesis of the condition. Virchow, Rokitansky and Chiari were acquainted with it, but accorded it scant attention in their works on pathology. Rayer in his Atlas illustrated two beautiful cases under the caption of *éruptions vésiculeuses*. In the latter part of the 19th century there was wider recognition of the disease, and the English observers Eve, Silcock, Sutton, Voelcker and Clark described cases, while Lubarsch, Fränkel, Markwald, Stoerck and others among the Germans, and Albarran, Tuffier, Cruveillier, Paul Barth, Lancereaux and others of the French writers recorded their experience with the condition. Not until 1902 does it occur in American literature when Harris studied three cases from the Johns Hopkins pathological series. All three were in aged persons, one a woman. Stow, in 1907, added a fourth case and Hibbs, in 1919, contributed a fifth. Recently the writer in doing routine autopsies at the Peter Bent Brigham Hospital encountered three cases in as many weeks and a detailed study of them forms the basis of this paper.

CASE I

Male, age 83 years, hospital number 21394. Entered the hospital July 24, 1919, in uremic coma. His immediate family history is interesting in that eight out of ten members died in their sixth to eighth decades. The past history is negative except that eight years previously he had been operated upon for prostatic trouble. Since then there had been constant slight trouble passing urine. One week before entrance he felt generally indisposed and soon developed symptoms of uremia. Twenty-four hours before admission acute retention occurred with spasm and twitching of face and arm muscles. There were marked signs of œdema of the lungs and a systolic murmur was heard all over the præcordium. An inlying catheter was inserted into his blad-

der. The urine examination showed an alkaline reaction, sp. gr. 1008 to 1011, a large trace of albumin; the sediment contained a few pus cells and triple phosphate crystals, but no epithelium. Phenolsulphonephthalein output O, urine output in two hours 12 c. c. The temperature ranged from 100° to 102°, respirations 30 to 40 per minute, pulse 95 to 120 per minute. His condition rapidly became worse and he died about 36 hours after entrance.

AUTOPSY DIAGNOSES

Gross.—Arteriosclerotic contracted kidneys. Double ureter (left). Hydronephrosis. Right and left ventricular hypertrophy. Pyelitis, ureteritis and cystitis cystica. Healed apical tuberculosis (left). Ruptured abdominal aneurism with extravasation of blood into the retroperitoneal tissues. Tuberculous ulcers of ileum. Chronic fibrous myocarditis. Atrophy of testicle (right). Generalized arteriosclerosis. Prostatic hypertrophy (median lobe).

Body is that of a well-developed, rather obese, aged man.

Primary incision shows about 3 cm. of normal yellow fat. The pectoral and recti muscles are uniformly paler than normal.

Peritoneal cavity contains about 100 c. c. of clear yellow fluid. The omentum, which is heavily laden with fat, is adherent to the sigmoid flexure. The liver extends to within 3 cm. of the lower right costal border and 1 cm. below the xiphoid. Just below the attachment of the root of the mesentery in the midline is an irregular retroperitoneal tumor, about 6 cm. wide, which bulges appreciably into the peritoneal cavity. The mesentery contains much fat and the lymph nodes are small.

Retroperitoneal Space.—There is a massive recent extravasation of blood into the retroperitoneal tissues, originating from a ruptured sacculated aneurism of the abdominal aorta about 5 cm. above the bifurcation. Blood has escaped on both sides and while confined strictly to the retroperitoneal region has infiltrated almost the entire right side posteriorly, extending from above and enveloping the right kidney and the tissues inferior to it including the ureter as far as the ureteral entrance in the vesical musculature. On the left side the extravasation extends from the upper level of the aneurismal tumor to the sigmoid flexure. All of the escaped blood is in the form of dark red, gelatinous clot.

Pleural Cavities.—The left lung is collapsed. The cavity contains about 150 c. c. of clear, straw-colored fluid. The apex is adherent to the pleura by tough, fibrous bands. There are several fibrous adhesions between the right lower lobe and the diaphragm. In the right side 50 c. c. of clear fluid are present.

Pericardial cavity contains about 20 c. c. of clear fluid. There are two polygonal plaques, 8 mm. wide, of thickening of the parietal pericardium overlying the anterior portion of the right auricle.

Heart.—Weight 490 gm. It is symmetrically enlarged. The left ventricle is markedly hypertrophied. A considerable amount of yellow fat lies along the coronary sulci and largely covers the intervening spaces. The right auricle is moderately dilated. The tricuspid valve is normal. On the free border of the anterior cusp of the mitral valve is an irregular, pale red nodule, 1 mm. at the base and 2 mm. in height. There is no demonstrable insufficiency. The cusps of the aortic valve are diffusely thickened with calcareous plaques on their facing surfaces. There is good approximation, however. The endocardium otherwise is smooth and pale. The coronary vessels are irregularly thickened, atheromatous change being most marked, with also a considerable loss of elasticity. The myocardium of the left ventricle shows several areas of fibrosis, the central portion being most affected, and narrow, pale, opaque, white lines leading outward from it in an irregularly radiating manner for 2 to 3 mm.

Lungs.—The right lung is emphysematous. The left lung is of similar appearance except that the apex presents a puckered, thickened area 2 cm. wide, which on section cuts with difficulty and has the appearance of a scar.

Spleen.—Weight 130 gm. Acute splenic tumor.

Gastrointestinal Tract.—The œsophagus, stomach, duodenum and jejunum are normal. In the ileum are two ulcers, each about 2 cm. wide, at the site of Peyer's patches, one 4 cm. and the other 10 cm. from the ileocecal valve. Viewed from the peritoneal surface, the base of each ulcer is greenish-black and surrounded by a zone of petechial hemorrhages. In the lumen these lesions have a crater about 2 mm. deep, bordered by an indurated ring of injected mucosa, but there is no undermining apparent. The base is grayish-green and is covered by thin slime such as is present elsewhere in the ileum. The large intestine shows no lesion.

Liver.—Weight 1880 gm. Its surface is smooth and slightly paler than normal. The cut surface shows the lobules fairly well delineated by pale red lines with the central portions yellowish-brown.

Gall-bladder is distended with greenish-black mucilaginous bile. The mucosa is normal. The ducts are patent.

Kidneys.—Weight of right 110 gm., left 160 gm. The right kidney is much smaller than the left. Both are embedded in much indurated perirenal fat. Two ureters, both of the consistence of a bronchus, lead from the left kidney to unite 4 cm. above the bladder where the lumen becomes narrowed and the consistence normal. The right kidney has a single ureter which is of similar external appearance to those of the left, but is surrounded by blood-clot from its having been enveloped in the massive retroperitoneal hæmorrhage from the ruptured aorta.

The right kidney is atrophic and has an irregular, coarsely granular surface from which the thickened capsule strips with some difficulty. The exposed surface is dull red and granular with several cortical cysts .2 to 1 cm. in diameter, projecting slightly above the surface, and containing a greenish mucoid secretion. The organ cuts with difficulty, owing to the great amount of fibrous tissue throughout. The cortex is pale red and thin, in many places being only 1 mm. in thickness. The glomeruli are much diminished in number and those to be seen are just barely visible. The pyramids show much distortion, with pale white opaque lines traversing them in various directions. The pelvic fat is much increased. The pelvis presents many pale, semi-translucent, bead-like projections 1 to 3 mm. wide, containing clear, thin fluid, usually closely arranged and found lining the calices, particularly those of the upper pole. Some of these are surrounded by red, hemorrhagic tissue, which continues to the ureteral orifice. The pelvis is not dilated, but the ureter is enlarged in its entire length by the presence of innumerable pale, cystic bodies 1 to 3 mm. in width, containing clear, watery fluid and which almost occlude the lumen. The ureter is literally studded with these bodies, though they become smaller and fewer as it traverses the bladder wall. A medium-sized probe can be passed into the ureter with difficulty and the passage of urine must have taken place by the process of seepage around the occluding cysts.

The left kidney, although larger than the right, shows no gross evidence of hydronephrosis. The surface markings are similar to those of the right kidney. The cortex is thin and scarred. The pelvic fat completely fills the pelvis and is closely approximated to the pyramids. The lining of the pelvis presents the same studded appearance as in the opposite kidney only to a more marked degree, the calices frequently being distended by the many cysts present. From the left kidney two ureters are given off, one from each pole. They are both enlarged and, until they become united about 4 cm. above the bladder, have an interior appearance like that of the right ureter.

There are none of these growths visible to the naked eye below the point of union of the two left ureters; and the common tube formed has a normal lumen, though slightly thickened walls.

Escape of urine from the left kidney must, too, have been by seepage through the strata of obstructing cysts.

The bladder is large and flaccid. The walls are moderately hypertrophied, the mucosa trabeculated. The posterior portion of the floor is speckled with round, miliary-sized, pale white areas, many of which have a central, pale, cystic eminence not unlike that of the smaller bodies observed in the ureters. The trigone is reddened. The ureteral orifices are not swollen and the passage of a probe is easy. The prostate seems to be present in its entirety and there is a moderate middle lobe hypertrophy. The prostatic urethra appears normal.

Testes.—The left is of normal size and "strings out" in a normal manner. The right testis is small, the tunica thickened, the seminiferous tubules being almost entirely replaced by connective tissue.

Adrenals are normal.

Aorta.—The ascending portion of the arch, although not dilated, shows several irregular thinned out areas from .3 to 2 cm. wide, to which pale red, elastic thrombi are attached. The edges are raised and appear to be composed of atheromatous deposit. Continuing along the aorta until the level of the renal arteries is reached, the same condition is seen with much roughening from projecting, jagged yellow plaques and diffuse intimal thickening with calcification.

About 2 cm. below the opening of the superior mesenteric artery on the left posterior wall is a sacculated aneurism about 4 cm. in depth. It is outlined by ragged, hard and yellowish, slightly raised, atheromatous-appearing tissue and the crater is filled partially with dark red recent thrombi and older gray elastic mural thrombi. A perforation exists about 1 cm. wide in the central portion and there has been considerable extravasation of blood, with dissection between the media and adventitia above to as far as the mesenteric artery and below to within 4 cm. of the iliac bifurcation. The surrounding connective and fatty tissue is infiltrated with blood, the entire mass being firm and elastic. The iliac arteries are tortuous and irregularly thickened with atheromatous and calcified plaques in their walls. The mesenteric, renal and hepatic arteries are of similar appearance and mural thrombi are present in some of the smaller branches of the mesenteric artery.

Microscopical Examination

Heart.—The sections show a considerable degree of coronary sclerosis and areas of fibroplasia in the interstices with atrophy of muscle fibers in these areas. There is rather marked brown pigmentation of the myocardium.

Lungs.—Negative.

Spleen.—Acute splenitis with marked elastoid degeneration of the arterioles.

Liver.—There are numerous necroses irregularly distributed as regards their position in the lobule, and usually involving two to five liver cells. Others are larger and in the peripheral zone. There is a moderate degree of portal sclerosis with infiltration by plasma and lymphoid cells. The branches of the hepatic artery show marked hyalin changes in the media.

Kidneys.—Both show a marked grade of chronic vascular nephritis. The vascular lesions consist of an advanced degree of intimal thickening of the renal arteries with hyalin changes in their walls, sclerosis of the arteriolæ rectæ, hyalinosis of the afferent arterioles of the glomeruli and all stages of similar change in the glomerular capillaries. Most of the glomeruli are completely fibrosed; the surrounding tubules are replaced by fibrous tissue in which are many lymphoid and plasma cells. There is atrophy and dilatation of other groups of convoluted tubules. In the medulla there is marked infiltration with mononuclear cells and polymorphonuclear leucocytes, many of the latter filling collecting tubules. Hyalin casts are present in most of the tubules in the pyramidal zone. A moderate degree of hydronephrosis is indicated by the dilatation of the collecting tubules and accumulation therein of albuminous fluid.

Ileum.—A section of the ulcer shows it to extend nearly to the muscularis, being rather sharply outlined there with slight undermining of the mucosa at one edge. Typical tubercles are present in the submucosa of the adjacent non-ulcerated portions and in the floor of the ulcer. Miliary tubercles are present in between the muscle fibers of the circular layer. Many vessels show thrombosis with organization and canalization.

Adrenals.—The arteries show much thickening of the intima and hyalinosis of the media. The cortical cells have a high lipoid content; certain areas show degeneration of cells and proliferation of fibroblasts in the intercellular spaces with migration of a few wandering cells.

Ureters.—Sections from the very cystic portions of the ureters at different levels show the same general picture. The projecting cysts are lined with low cuboidal epithelium in two or three layers along the base, but only a thinned single layer in the greater part of its inside circumference. The contents are a more or less homogeneous eosin-staining material which has retracted somewhat from the walls. In it are numerous large, round or elliptical bodies with dark pyknotic inclusions which suggest nuclear fragments. Fat droplets are present in some. Along the periphery are many degenerated epithelial cells and desquamated normal-appearing cells of the lining. The granular nature of portions of the cystic contents with the degenerated cells along the border make it appear probable that much of the material in the cysts has that origin. A thin connective-tissue envelop surrounds the cysts, but no definite epithelial elements can be made out. The origin of these growths seems very likely from "nests" of epithelial cells of the type of the ureteral lining, as these can be seen in the less involved parts and in the bladder, lying in the mucosa. These "nests" of cells are surrounded by a connective-tissue stroma rich in blood-vessels and in which lymphoid cells are often present in numbers. There is proliferation of these cells followed by degeneration and cyst formation with swelling toward the surface. All these stages are found. The smooth muscle of the ureter is atrophied and invaded by considerable connective tissue.

CASE II

Male, age 74 years, hospital number 21829. A Civil war veteran who entered the hospital complaining of shortness of breath and swelling of the abdomen and limbs. His past history was irrelevant, except that for the past 15 years he had had frequent nycturia. His present illness had begun about two years previously with shortness of breath on exertion. Other symptoms of decompensation of the heart had occurred and recently anasarca had gradually developed. Upon physical examination he was very dyspnœic and cyanotic, with respirations Cheyne-Stokes in character. There was general anasarca. The heart was in auricular fibrillation. The peripheral arteries were markedly thickened. Blood-pressure 188 systolic, 116 diastolic.

Under the Karell diet and digitalis he lost 3.7 kilos in weight. Two thousand cubic centimeters of fluid were removed from the right chest. He became steadily weaker. Venesection was done, 300 c. c. of blood being removed. On the fourth day he died. Clinical pathology: Urine on two examinations, amber, acid, sp. gr. 1018 to 1020, albumin a trace. Blood examination including the Wassermann was negative.

Autopsy Diagnoses

Gross.—Chronic myocarditis. Acute hæmorrhagic necrosis of pancreas. Double hydrothorax. Hydropericardium. Ascites. Œdema of extremities. Left and right ventricular hypertrophy.

Healed abscesses of left kidney. Cystic cystitis. Double hydrocele. Arteriosclerosis.

Body is that of an aged white man, rather obese. There is marked pitting œdema of the lower extremities.

Primary incision shows panniculus about 3 cm. in thickness. There is moderate œdema of the chest and abdominal walls.

Peritoneal cavity contains about 200 c. c. of yellowish fluid tinged with blood. There are no adhesions. The liver extends 4 cm. below the right costal border and 3 cm. below the ensiform. The mesenteric lymph nodes are considerably enlarged, due to œdema.

Pleural Cavities.—The left contains 700 c. c. of straw-colored fluid; the right, 900 c. c. of similar fluid.

Pericardial cavity contains 120 c. c. of yellow fluid. There is no displacement of the heart.

Heart weighs 700 gm. Measures *in situ* 17 x 11.5 cm. The left ventricle is greatly hypertrophied, the right ventricle moderately hypertrophied. The right auricle is dilated. The tricuspid, pulmonic and mitral valves are normal. The aortic valve leaflets show no distortion although the mural halves of the cusps are composed chiefly of a gritty, calcareous material. The endocardium as a whole is of the normal red color. Sections through the left ventricle in different places show the myocardium uniformly of the normal red color, firm, and without evidence of fibrosis or fatty infiltration. The coronary arteries are considerably thickened. The lumen, as far as it can be traced, is of normal width. Atheromatous plaques are numerous along the course of the coronary arteries and in places there is some calcification in these deposits.

Lungs.—Weight of right lung 600 gm., left 540 gm. Both are moderately emphysematous, and the posterior portions are full of œdematous fluid.

Spleen.—Weight 210 gm. It is enlarged, purplish-red in color. The surface is tense. On section the pulp is dark red and firm.

Gastrointestinal Tract.—The mucosa of the œsophagus, stomach and duodenum is dull red, especially along the tips of the folds. The contents are thin fluid in nature. The rest of the intestinal tract shows no lesion.

Pancreas.—There is a considerable amount of congestion in the more central portions and along its entire length. The lobules are prominent, although there is considerable œdema throughout the organ.

Liver.—Weight 1710 gm. Its surface is deep, reddish-brown and rather tense. Capsule in places is rather opaque and thickened. Upon section there is throughout a somewhat nutmeg appearance. The central veins appear congested. In one place, about 5 mm. below the capsule in the anterior surface of the right lobe, is a round, white area about 3 mm. in width which appears calcified.

Gall-bladder shows considerable fluid beneath the serosa. It is swollen and œdematous and contains about 30 c. c. of a thin, black bile. The ducts are patent.

Kidneys.—Weight of right 250 gm., left 240 gm. The capsule strips easily from a very slightly granular, dull red surface. The cortex varies in width from 4 to 8 mm. The surface as a whole is considerably congested and red in appearance. The glomeruli are very prominent as dull red dots projecting above the cut surface. The pyramids have dull red striations alternating with slightly brighter red lines. The pelvis shows no lesions, the lining being smooth and white. The left kidney shows here and there in several of the pyramids about 15 mm. above the tip, round, white, encapsulated lesions about 3 mm. in width. They cut with considerable resistance. A frozen section of one of these shows it to consist almost entirely of vascular fibrous tissue. These lesions probably represent healed abscesses.

Adrenals are normal.

Ureters are opened at different levels and appear normal.

Bladder contains about 100 c. c. of turbid urine. The mucosa about the ureteral orifices and in the trigone present numerous small vesicles 1 to 1.5 mm. in width and containing a clear fluid. These cystic bodies are more numerous in the trigone than elsewhere and the trigone itself is somewhat injected.

Genitalia.—There is a double hydrocele. The testes string out normally.

Aorta is of normal elasticity throughout its entire length although there are numerous large atheromatous plaques, especially about the opening of the intercostal arteries. To some of these plaques flecks of fibrin are attached. The iliac arteries, 4 cm. below the bifurcation in the posterior walls, are much thickened. There is a good deal of puckering of the intima about these areas.

Heart.—A section through the left ventricle wall shows the muscle fibers hypertrophied to a marked degree. There is moderate interstitial œdema and the capillaries as a whole are congested. The muscle of the walls of the arteries is hypertrophied, but the lumen is not narrowed and there is but very slight evidence of fibrous myocarditis.

Lung.—The alveolar capillaries are moderately congested and in the alveoli is considerable œdematous fluid. Hemosiderin-laden phagocytes are numerous in many alveoli.

Spleen is typical of chronic passive congestion.

Liver.—There is marked central zone congestion with pressure atrophy of the liver columns of the congested areas. Endothelial leucocytes are numerous in many of the portal spaces. The capsule is diffusely thickened and in one place is a patch of perihepatitis in which are many mononuclear cells and fibroblasts.

Pancreas.—The section shows a very marked degree of acute hemorrhagic necrosis superimposed upon an old chronic interstitial pancreatitis. The lobules are still defined by fibrous tissue in which massive hæmorrhage has occurred. The acini in most of the lobules show acute degenerative changes. There is a diffuse increase in connective tissue throughout many lobules. Fat necrosis has occurred in and immediately about the areas of hæmorrhage. A feature of the section is the entire lack of acute inflammatory exudate about the necrotic areas, only a few lymphoid cells being seen beneath the capsule in places. The islands of Langerhans are destroyed, except a few in the peripheral, more normal-appearing portions of a few lobules. The arteries are markedly sclerosed and although no actual rupture can be made out, a few show R. B. C. infiltration between media and adventitia. The picture is that of a "pancreatic apoplexy" or Chiari's "acute hemorrhagic pancreatic necrosis." The pancreatic duct was not investigated thoroughly enough to rule out obstruction to it.

Aorta.—A section of the aorta is taken through a typical atheromatous plaque of large proportions. Fat crystals are present in great numbers in the thickened intima. The elastica is frayed out at the margins. About the vasa vasorum mononuclear cells have infiltrated in numbers.

Kidney.—There is marked congestion and œdema of both cortex and medulla, with considerable albuminous granular material in the glomerular spaces. The glomeruli as a whole deviate but slightly from the normal, an increased number of nuclei in the tuft, endothelial cells and occasionally lobulation of the tuft being seen. Beneath the capsule, which is somewhat thickened, are several foci of lymphocytes and similar foci are seen scattered through the cortex, and in the vicinity of these interstitial fibroplasia has occurred. The afferent arteries of the glomeruli show quite uniformly hyalin thickening of their walls and the larger arteries a marked degree of sclerosis. Hyalin casts are present in many collecting tubules. The tubules in the medulla show moderate to fairly marked changes of hydronephrosis. The pelvic epithelium has largely been destroyed and replaced by a

vascular granulation tissue rich in plasma, lymphoid and eosinophilic cells.

Ureters.—The lesions may be summed up as a marked chronic inflammation of the mucosa with cell "nests" and crypt formation, atrophy and fibrosis of the circular and longitudinal muscle bundles. All levels are involved in these changes. In the upper half the most marked changes have occurred. The epithelial lining has largely been destroyed, leaving exposed a very vascular connective tissue in which are large numbers of mononuclear phagocytes, small lymphocytes, plasma cells and a few polymorphonuclear leucocytes. A few short, thick bacilli are visible with Goodpasture's acid-fuchsin stain. Embedded in this inflammatory tissue are numerous "nests" of epithelial cells, some directly beneath the surface, others connected with it by a very narrow strand of epithelial cells. Most of these "nests," however, have lost all connection with the lumen of the ureter and lie isolated (as serial sections show) in the tunica propria. In no case has herniation through or growth into the muscularis occurred. These "nests" vary much in size. Many are of from 10 to 30 cells, others are slightly larger and show degeneration in the center with consequent lumen formation. The individual cells are polyhedral or more or less columnar, varying with the amount of degeneration in the center. Several sections show large cysts bulging into the lumen of the ureter from all sides. These are lined with a transitional to low columnar epithelium, and contain a basophilic or neutrophilic material, in some cysts homogeneous like colloid, in others granular and containing desquamated epithelium much like the picture of a follicle of an old hypertrophied prostate.

The circular and longitudinal muscle fibers are atrophic; many contain large, clear vacuoles about the nucleus. The muscle fasciculi have been invaded by connective tissue in such amount that many contain only a few muscle fibers, the great part having been replaced by fibrous tissue. The arteries show moderate sclerosis.

In the lower half of the ureters the histogenesis of the cystic condition is well brought out. The lining epithelium is still preserved, but excessive infolding of the mucosa has produced deep folds and crypts and many smaller and shallower infoldings. The subepithelial tissue or tunica propria is made up of tissue in which are numerous fibroblasts, wandering tissue cells, lymphocytes and a few polymorphonuclear leucocytes. This inflammatory tissue in many instances is seen to have extended across where the upper edges of the folds meet and cut off groups of epithelial elements from the lumen of the ureter.

These "nests" of cells have no basement membrane nor any of the characteristics of true glands. The same degree of muscular atrophy and fibrosis is seen in the lower half as in the upper half of the ureter.

Bladder.—The lining epithelium is still present in a few places in the section, as a fairly well-defined transitional type. It has largely disappeared, however, and been replaced by a very vascular chronic inflammatory tissue in which are large numbers of lymphoid and plasma cells and in one section are two rounded nodular prominences composed almost entirely of lymphoid cells.

The epithelial lining cells show very strikingly the formation of cell "nests." Deep infolding is observed in several places and in others the upper portions have fused owing to the overgrowth of inflammatory tissue and the "nests" have thus been cut off. Some of these contain a lumen due to degeneration in the central portion.

The smooth muscle in the bladder shows moderate hypertrophy and invasion by much connective tissue. The blood-vessels of the muscularis are congested and wandering cells are present in various portions.

Sections from the posterior wall, trigone and prostatic urethra show marked chronic cystitis with numerous small epithelial "nests" cut off from the surface by the overgrowth of granulation tissue. A few projecting cysts of small size are seen in sections of the posterior border of the trigone. The glands of the prostatic urethra contain much desquamated epithelium and a moderate number of corpora amylacea.

Testicle.—There is marked atrophy of the cells of the tubules, although an occasional spermatozoon is seen. The basement membrane of the tubules is markedly thickened and the arteries show advanced sclerosis.

Microscopical Diagnoses

Acute hemorrhagic pancreatic necrosis. Chronic fibrous myocarditis (slight). Cardiac hypertrophy. Chronic passive congestion. Chronic pyelitis. Healed cortical abscesses of kidney. Chronic ureteritis and cystitis cystica. Hydronephrosis (moderate). Chronic perihepatitis. Atrophic orchitis. Generalized arteriosclerosis.

CASE III

Male, age 66 years, hospital number 21088. Entered the hospital very drowsy, with swelling of the legs and shortness of breath. Two years previously he had had a prostatectomy following urine retention and nycturia regarding which a note from Dr. George Gilbert Smith says:

"On May 21, 1917, I did a perineal prostatectomy under spinal anæsthesia. A very large, typical adenomatous prostate was removed, also a stone in the bladder. His convalescence, except for an epididymitis, was uneventful. At that time he had a blood-pressure of 200 with cardiac enlargement and a systolic murmur.

"I saw Mr. T. again on July 12, 1918. He was complaining of hæmaturia. I cystoscoped him and found that bloody urine was coming from the left ureter. His blood-pressure was 240. It seemed to me that his hæmaturia was due to nephritis."

Otherwise his past history was unimportant. His present illness had begun about six months before with hæmaturia, which had increased until at entrance he was passing nearly pure blood. His legs had begun to swell four months later but the swelling was somewhat relieved by digitalis. He was dyspnœic on exertion and the œdema of his extremities increased steadily. Physical examination showed general anasarca, much wasting and an enlarged heart with poorly transmitted sounds. There was a markedly urinous odor to the breath.

Under treatment his heart action improved and most of the œdema disappeared. The blood-pressure ranged for many days from 150 to 190 systolic and 90 to 130 diastolic. The blood urea averaged about 45 mg., but reached 74 mg. at one time with only a trace of phenolsulphonephthalein excreted. The urine always showed a large amount of albumin, hyalin and granular casts. After being in the hospital 75 days he developed gangrene of the right foot with absence of pulsation in the popliteal artery of that side. He showed Cheyne-Stokes respirations almost constantly, the temperature rose from 99° to 102° and shortly before death to 107° with signs of pneumonia. He died on the 77th day.

Autopsy Diagnoses

Gross.—Chronic myocarditis with cardiac hypertrophy. Bilateral broncho-pneumonia with purulent bronchitis. Thrombosis of right auricular appendage. Bilateral hydrothorax. Sclerosis of the coronary arteries. Senile aortic arteriosclerosis. Bilateral pyonephrosis with marked atrophy of the renal medulla and cortex accompanied by bilateral renal calculi occupying the renal pelves and extending down into the ureters. Bilateral perinephritis. Pyelitis, ureteritis and cystitis cystica. Chronic fibrous perisplenitis with passive congestion of spleen. Passive congestion of the liver. Cholelithiasis. Petechial gastric hæmorrhages. Hæmorrhagic colitis. Visceroptosis. Gangrene of the

lower right leg with thrombosis of the anterior tibial artery with possible involvement of the external popliteal.

Body is that of a very emaciated male, white adult. The skin is dry and thick. The lower part of the right leg and the right foot present a bright red discoloration, the hue gradually increasing in intensity distally from the calf. This entire distal portion of the right lower extremity is red, slightly boggy and the skin covering it is moist and desquamating. Upon excising the proximal portion of the anterior tibial artery it is found to have been recently thrombosed, the lumen being occluded by a soft red blood-clot for a distance of several centimeters with probably extension into the external popliteal artery. An organized mural thrombus in the anterior tibial artery in the lower tibial region occludes about one-third of the lumen.

Primary incision discloses very little subcutaneous fat and markedly atrophic pectoral and abdominal muscles.

Peritoneal Cavity.—There are numerous adhesions of the omentum to the sigmoid flexure, to the liver and the right lateral abdominal wall. The parietal peritoneum is elsewhere smooth and glistening. There is marked ptosis of the viscera, but especially of the cæcum, the transverse colon and the sigmoid. The cæcum and the appendix have entirely descended into the pelvic cavity.

Pleural Cavities.—The left pleural cavity contains 850 c. c., the right 540 c. c. of reddish fluid.

Heart.—Weight 650 gm. It is markedly hypertrophied. The pericardium is smooth and does not show any roughening or adhesions. The myocardium of the left ventricle measures approximately 2 cm. in thickness. It is firm, pale, but does not show any particular increase of connective tissue. The endocardium is smooth with here and there evidence of some fat. There are no valvular lesions and the cardiac chambers are empty aside from a small, fragile, reddish thrombus in the right auricular appendage. The coronary arteries are somewhat sclerosed as is also the proximal portion of the aortic arch.

Lungs.—The right lung weighs 545 gm., the left lung 405 gm. The external appearance of both lungs is grayish-white. Both crepitate upon pressure. Upon section, the cut surface is grayish and moist. Upon pressure, frothy fluid escapes from the alveoli and puriform matter runs from the larger bronchioles. In the lower lobes there are areas of firmer consistence, reddened, and standing out in contrast with the surrounding lung tissue. In several places along the periphery of the lung there are areas of firmer consistence which do not crepitate upon pressure and on section show a reddened, moist surface.

Spleen.—Weight 170 gm. The external surface of the spleen is covered with numerous small white masses appearing like beads. These are embedded in the capsule. The spleen sections easily and the cut surface is dark red and of firm consistence.

Gastrointestinal Tract.—The œsophagus is normal. In the fundus region of the stomach there are present groups of petechial hæmorrhages. There are probably as many as 20 of these, the individual hæmorrhages being about the size of the head of a pin. The duodenum, jejunum and ileum are normal aside from the ptosis. The cæcum lies in the pelvic cavity and is greatly distended with fecal material. The ascending colon is not remarkable, but the transverse colon is markedly ptosed and contains very hard, scybalous fecal matter. Similar scybalous ball-like masses are found in the descending colon, the sigmoid and the rectum. The external appearance of the colon is dark and congested. The mucosa is markedly reddened, while in four or five places in the mucosa of the transverse colon there are definite hæmorrhagic areas about 1 cm. in size.

Pancreas.—Normal.

Liver.—Weight 1560 gm. It is moderately congested. The gall-bladder contains about 20 c. c. of dark brown bile and four small gall-stones. The gall-ducts are patent.

Kidneys.—Each kidney weighs 285 gm. *In situ* they are very irregular in outline, covered and embedded in a great deal of indurated perirenal fat, while in the pelvis of each kidney a hard, rock-like mass can be palpated, apparently directed downward toward the ureter. The ureters also appear to be œdematous, enlarged in circumference, soft and boggy to feel. In extricating the kidneys great difficulty is experienced, as they do not shell out of the perirenal fat as usual, but have to be dissected away. In the attempting to remove this it is found that the renal capsule is also so adherent that it strips with difficulty from the surface leaving a red, granular, irregular surface, showing here and there cicatricial contractures and depressions. Separating rough granular areas are portions of cortex, smooth, depressed and fluctuant. Upon sectioning, the kidneys both present a strikingly similar picture. The pelvis of each is occupied by a large, hard, light brown stone securely anchored in place by its ramifications in the renal calices and directed downward into the opening of the ureters. There is very marked œdema of the pelvic fat. The pelvic lining is congested, and there are numerous blotchy hæmorrhages beneath. The renal calices are seen to be greatly enlarged, several of them being distended with semifluid puriform material. The overlying medulla and cortex are but a thin sheet. In other places the cortex measures as thick as 5 mm. and is very congested.

Ureters.—Both ureters and the distal portion of the pelves when opened have an inner surface made irregular by the presence of numerous vesicular growths, in size varying from a pin-head to 3 mm. and separated about .5 to 1 cm. from each other. These vesicles are colorless and contain a thin, turbid fluid, which spurts on opening. Many of these bodies are pedunculated and hang downwards in the ureters like minute pears. They diminish in number gradually toward the bladder and about 3 cm. above that organ they are not visible. The remaining mucosa is pale and granular. The ureteral wall as a whole is thicker than normal.

Bladder contains about 50 c. c. of turbid urine. The ureteral openings are patent. Scattered irregularly over the mucosa, more especially just outside the trigone, can be seen an occasional projecting cystic body about .5 mm. in width. The bladder mucosa, however, is of normal appearance except for these cysts and slight injection of the trigone.

Aorta shows marked senile arteriosclerosis.

MICROSCOPICAL EXAMINATION

Heart.—The muscle fibers are moderately hypertrophied and many contain hydropic vacuoles. There is a diffuse increase in interstitial connective tissue and beneath the endocardium a few irregular patches show a considerable degree of fibrosis with atrophy of the muscle fibers. The coronary arteries present various grades of sclerosis, many have hyalin changes in their media and one shows early calcium deposition about the hyalinized layer. The capillaries as a whole are congested and there is moderate interstitial œdema.

Lung.—There is one section which is not remarkable except for rather marked sclerosis of the branches of the pulmonary artery and the presence of a spicule of bone about 1.5 mm. in width lying next to an interlobular septum in which there is a considerable amount of carbon pigment. Throughout the section large mononuclear cells containing hemosiderin granules are quite numerous in the alveoli.

Spleen.—The pulp is markedly congested and contains many large mononuclear phagocytes containing fat vacuoles. The lymphoid tissue has largely disappeared. The arteries of the malpighian corpuscles show pronounced elastoid degeneration.

Liver is characteristic of the early reparative stage following the central necroses of chronic passive congestion.

Kidneys.—They are remarkable for showing both an extreme grade of arteriosclerotic change and pyelonephritis with cortical abscesses. Most of the glomeruli are completely fibrosed and the afferent arterioles and larger arteries show very marked sclerosis. There has occurred marked atrophy of the cortical tubules with great interstitial fibroplasia and infiltration with lymphoid, plasma cells and polymorphonuclear leucocytes. There is marked congestion throughout the organ, but most conspicuously in the medulla. Several small abscesses are present in the boundary zone and in many of the collecting tubules are calcified or hyalin casts. The pelvic epithelium has entirely disappeared and very vascular granulation tissue forms the lining of the pelvis.

Gastrointestinal Tract. Stomach.—The mucosa of the fundus shows numerous hæmorrhages into the folds from rupture of capillaries. The hæmorrhages vary in size, the largest occupying the greater part of two contiguous folds. The lining epithelium is desquamated from over the areas and the mucosa as a whole is very atrophic. There is no cellular reaction about the hæmorrhages.

Duodenum.—There are a few very small hæmorrhages in the submucosa.

Large Intestine.—There are many hæmorrhages similar to those in the stomach only more extensive, involving the interstices of several adjoining crypts.

Pancreas.—There is a moderate amount of fatty infiltration between the lobules. The parenchyma is normal.

Ureters.—Sections from the upper third of each ureter show the lining epithelium in many places replaced by a chronic inflammatory tissue. Many "nests" of cells similar to the lining epithelium are found in the connective tissue of the mucosa. Many of these have undergone cystic degeneration and several project prominently above the surface so as to partially obliterate the lumen. The cysts are lined with a single to triple layer of epithelial cells and covered by a thin, fibrous envelop. The process appears to be due to the marked infolding of the mucosa, the muscle fibers being very atrophic, and connective tissue being increased in amount both in the tunica propria and between the atrophic muscle bundles. The tips of some folds have become closely opposed and granulation tissue has bridged the interspace cutting off "nests" of cells which ordinarily line the deeper portions of the crypts. The arteries show moderate sclerosis.

Bladder.—The mucosa has been largely replaced by a vascular granulation tissue, the epithelium being entirely absent in the section except in a few places near the ureter where a few "nests" with cysts appear. The content of the cysts is a more or less homogeneous material, the peripheral portions eosinstaining and the central parts deeply basic. Fat-laden phagocytic cells and nuclear fragments are numerous in the cysts. The smooth muscle shows evidence of previous hypertrophy followed by extensive fibrosis between the fasciculi and individual muscle fibers.

Microscopical Diagnoses

Pyelonephritis with cortical abscesses. Arteriosclerotic nephritis. Chronic fibrous myocarditis. Generalized arteriosclerosis. Coronary sclerosis and calcification. Cardiac hypertrophy. Multiple hæmorrhages into mucosa of stomach, duodenum and large intestine. Chronic passive congestion of liver with central necroses. Chronic ureteritis and cystitis cystica. Bone metaplasia in lung.

Origin of Cysts of the Urinary Tract

The literature regarding pathogenesis is very abundant in hypotheses. This is in a degree due to the finding in one case of cysts in the kidney, ureter and bladder, in another cysts in the pelvis and ureter, in others only in the bladder in the region of the trigone or prostatic urethra. The similarity of the epithelium lining these organs was apparently not fully appreciated. All the explanations so far offered for the condition may be divided into three main groups: (1) That the cysts are parasitic in nature; (2) that they are derived as retention cysts from pre-existing glands in the pelvic, ureteral or vesical mucosa; and (3) that they originate from the cell "nests" of von Brunn.

The idea that the cysts are due to parasites had supporters for many years, but toward the end of the 19th century was almost entirely discarded, no cases having been proven, although the possibility was not denied. The variety of parasites declared responsible for the cystic condition served to throw legitimate doubt about the whole argument. Morgagni interpreted the cortical cysts in small granular kidneys as hydatid and those of the ureters were also thus considered. In Eve's case psorosperms or pseudonavicellæ of the Gregarinidæ and in Sutton's case coccidium oviforme were thought to be the causative agents. Pisenti and von Kahlden were also in favor of a protozoan etiology. In Fig. 3 the four cysts to the right contain in the colloid matrix numerous rounded or oval bodies which seem identical with Eve's "psorosperms." They are, however, like no known parasite, being composed of a central mass of pyknotic nuclear substance embedded in material of a fatty or lipoid nature with usually no definite limiting membrane. In the cyst on the left these bodies are present in such numbers that many have fused to form irregular granular masses with nuclear fragments undoubtedly derived from broken down epithelium or leucocytes. Further doubt was thrown upon the possibility of these bodies being parasites by the work of Gilchrist, who showed that degeneration of epithelium gives rise to particles which simulate and have been called psorosperms, organisms of blastomycotic dermatitis and other allied affections.

Virchow and Chiari believed that the cysts were retention cysts from pre-existing glands in the mucosa of the ureter or bladder in which a catarrhal inflammation usually existed and which was regarded as the cause of the blocking of the gland ducts. Litten was of a similar opinion. In the older text-books of histology, mucous glands were usually mentioned as occurring normally in the ureter, particularly in the upper third. Wendt, Hamburger and Egli described gland-like structures in the mucosa; but recent opinion is that normally there are no true glands in the mucosa of the pelvis, ureter or bladder of man. What gland-like formations have been found were apparently due to proliferation of the surface epithelium or excessive infolding of the mucosa. In the region of the prostatic urethra aberrant urethral glands and prostatic follicles were considered by Lubarsch as possible forerunners of macroscopic cysts.

The view finding widest acceptance in recent years is, with various slight modifications, that the cysts are derived from groups of epithelial cells which become isolated from the

lining of the mucosa and lie in the tunica propria. These epithelial groups are known as the cell "nests" of von Brunn, as this investigator gave them the first careful consideration, although Unruh, Egli and Hamburger had previously noted their presence in the ureter and pelvis. Von Brunn working with organs of condemned criminals was unable to demonstrate them in the renal pelvis, but in the ureters and bladder he described grape-like adenoid bodies composed of cells similar to the lining epithelium lying in the tunica propria. These at first were connected with the overlying epithelium and ran vertical to it, later assuming a more parallel position and finally becoming detached to form "nests." He believed, then, that these "nests" were isolated groups of cells derived from invaginations and crypts of surface epithelium which Hamburger and others regarded as mucous glands.

The occurrence of von Brunn's cell "nests" appears to have a definite relationship to the age of the individual. Aschoff states that no "nests" of von Brunn occur in the ureters of the newly born or in early life, and that they are inconstant in adult life. Markwald found ureteritis and cystitis cystica in a newly born, and claims with Aschoff that inflammation is not *first* necessary to originate the "nests" and crypts. In the ureters of eight infants from five days to eighteen months old the writer was unable to find any "nests," sections being taken from ten levels of each ureter. These findings then are in agreement with Aschoff's, and the writer cannot but believe that in Markwald's case the "nests" must have had an inflammatory origin.

However, text-books of histology describe them as found normally in adult ureters. No doubt a few occur in middle life, but it is also true, at least in the writer's experience, that they increase in number with age, being most plentiful after 50. It is a striking fact that ureteritis cystica is a disease chiefly of old age, over 95 per cent of cases occurring after the 50th year, and a large number in the seventh and eighth decades. The figures as to sex are about equally divided.

Stoerck insists there must *first* be inflammation to cause cell "nests" even though all traces of it disappear. He calls attention to the fact that there is nothing analogous to von Brunn's "nests" in other mucous membranes of the body in extra-uterine life. However, the heteroplasia of epithelium lining the gall-bladder is a somewhat similar phenomenon. Saltikow met with three cases of ureteritis cystica and four cases of pyelitis cystica, and in six of these cystitis cystica was present. Of 15 cases of cystitis cystica diagnosed macroscopically four were in patients 30 to 50 years of age and nine occurred between the 60th and 87th years. He was of the opinion that von Brunn's "nests" were associated practically always with inflammation, that they were not normal structures. Herxheimer, also, emphasized the importance of the inflammatory factor. These authors believed that through degeneration of these groups of epithelial cells cut off from the surface the cysts of the pelvis, ureter and bladder arose. Lubarsch attributed their origin to three sources: (1) Mucous crypts; (2) epithelial "nests" of von Brunn; and (3) in the bladder from abnormally placed urethral glands. In 3000 autopsies he found cysts of the renal pelvis twice, and in the ureter four times, all in patients over 70 years of age.

Certain experimental work is of interest in this connection. Giani in studying tuberculosis in rabbits inserted gelatin capsules into the bladder through a suprapubic cystotomy and found that cell "nests" and cysts were formed at the site of injury. Cysts were also produced by irritation of the mucosa with a Volkman spoon.

Garrè, quoted by Buerger, describes "traumatic" epithelial cysts, the "atheromatous" cysts of the Germans, as occurring on the volar aspect of the hand and fingers from pieces of epithelium becoming mechanically displaced in the deeper tissues. Kaufman buried pieces of epithelium of the cock's comb and sutured the edges together, cysts being formed. Sutton has termed such implantation cysts. These traumatically displaced bits of epithelium are in many ways analogous to the cell "nests" in the pelvis, ureter and bladder, where the transformation into cysts is also accomplished.

Some correlation of the various views on the pathogenesis of cystic ureteritis, pyelitis and cystitis is necessary, although modern opinions do not show wide variance. The symptomatology is obscure. Cysts in the pelvis and bladder probably give no symptoms. In a narrow muscular tube like the ureter a moderate number of cysts might conceivably interfere with normal peristalsis. When they are in such numbers as in Case I, they no doubt are able to produce hydronephrosis *per se*, although frequently there has been a history of urinary calculi which might account for the hydronephrosis present. Examination of the urinary sediment has been of no help in diagnosing the lesion.

The writer's three cases were all in old men, two with a history of prostatic trouble and the third with bilateral renal calculi and pyelonephritis. The kidneys of all three showed advanced arteriosclerotic nephritis. There was generalized arteriosclerosis, particularly of the ureteral and vesical arteries. The photomicrographs show plainly the histogenesis of the cysts of the ureter and bladder. The arteries of these organs show much thickening and there are muscular atrophy and very marked fibrous myositis. These lesions possibly produce a degree of atony to account for the subsequent excessive infolding of the mucosa. Hypertrophy of the myoureter occurs after obstruction, to be followed later by the invasion of fibrous tissue. An increase of fibrous tissue throughout the tunica propria takes place, apparently an upgrowth toward the lumen to a considerable extent, and numbers of epithelial "nests" are formed. Many in addition originate through the superimposing of an infection with healing over of tips of folds of mucosa by granulation tissue. Ureteritis cystica in young individuals probably originates from cell "nests" formed in this manner. The inflammatory irritant causes both proliferation and degeneration of epithelium (mitotic figures may be seen in "nests" (Saltikow)), and the degeneration with transudation of fluid forms cysts which increasing in size come to bulge into the

lumen. With the inflammatory thickening of the tunica propria the elastic tissue practically entirely disappears from this layer and is greatly decreased in amount in the other laminæ as well.

Cystic inflammation of the pelvis, ureter and bladder, then, is a condition about which the following facts seem established: First, it is primarily a disease of old age; second, it occurs in persons of either sex in whom a history of urinary tract disturbance or definite inflammation can be elicited; third, the cysts arise from degeneration of the lining epithelium, particularly that which has become cut off from the surface of the mucosa, the "cell nests" of von Brunn. The condition has occurred in several cases of double ureter and one of the writer's patients had this anomaly.

The profound disturbance in the epithelialization of the ureter incident to the formation of cell "nests," their proliferation and degeneration, and the almost constant factor of senility makes it indeed surprising that primary epithelial tumors of the ureter are so rare. Vesical polyps frequently contain many isolated groups of epithelial cells corresponding to von Brunn's "cell nests" and to them has been attributed an inflammatory origin in consequence (Saltikow).

Having in mind the large numbers of cell "nests" of von Brunn in the ureter and bladder of senile individuals and the high incidence of infections of the urinary tract in the aged, the writer believes that cystic inflammation of these organs is relatively common and not rare, as the literature seems to indicate.

Summary

1. The condition described is a cystic inflammation of the pelvis, ureters and bladder.

2. It occurs in persons of either sex, in 95 per cent of cases in senile, arteriosclerotic individuals from whom a history of previous urinary inflammation or other disturbance can be obtained.

3. Three typical cases are reported in detail, all in aged men, two of whom had a history of prostatic trouble and the third bilateral pelvic calculi. In one a double ureter was present.

4. The pathogenesis may be epitomized as follows:

(a) In the aged, arteriosclerosis of the ureteral and vesical arteries occurs and is followed by muscular atrophy, fibrous myositis and loss of elastic tissue leading to atony of the ureter and bladder.

(b) By the marked infolding of the mucosa which follows, with fibroplasia in the tunica propria, many cell "nests" of von Brunn are formed.

(c) An inflammatory irritant, usually from the pelvis or bladder, causes the formation of granulation tissue which heals over apposed tips of mucosal folds to produce more cell "nests" (this being probably their only source in young individuals).

(d) The same irritant produces moderate proliferation of the isolated epithelial cells, followed by central degeneration and fluid transudation, thus giving rise to microscopic and macroscopic cysts.

5. In view of the large number of cell "nests" of von Brunn in the ureter and bladder of senile individuals and the high incidence of urinary tract infections in the aged, the writer believes that cystic inflammation of these organs is relatively common in this class of patients.

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EXPLANATION OF PLATES

Figs. 1 and 2 are gross photographs. In Fig. 3 the section is stained with Mallory's aniline blue connective-tissue stain; in all the others Mallory's methylene blue and eosin was used. Fixation was in Zenker's fluid.

FIG. 1.—Case I. Kidneys, ureters and bladder. The right kidney is atrophic and both have undergone extreme arteriosclerotic changes. The pelves and ureters show the extent of the cyst formation. The left ureter is double.

FIG. 2.—Double cystic ureter of Case I. The macroscopic cysts suddenly cease at the junction of the ureters. Microscopic cysts are present as far as the vesical orifice.

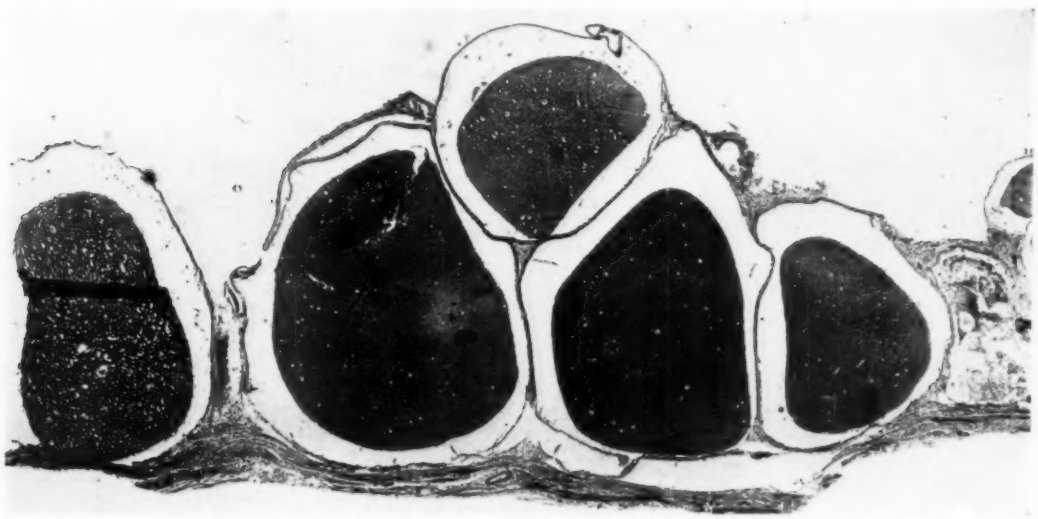

FIG. 3.—Longitudinal section of ureter from Case I, ×12. The thin-walled cysts are filled with a colloid material in which are bodies formerly mistaken for protozoa, but which consist of nuclear fragments and cellular debris. Fixation has caused the cyst contents to shrink away from the walls.

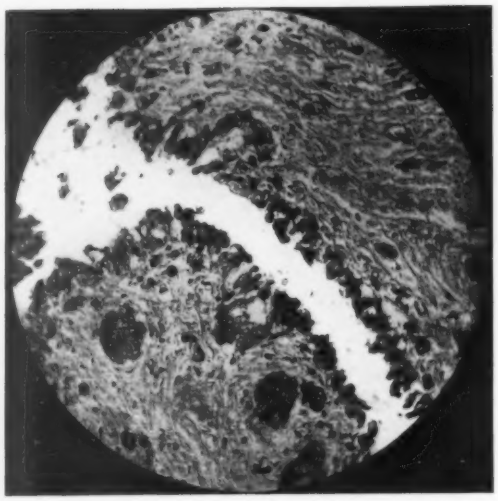

FIG. 4.—Section of the mucosa of ureter from Case II, ×75. The formation of the cell "nests" of von Brunn is shown.

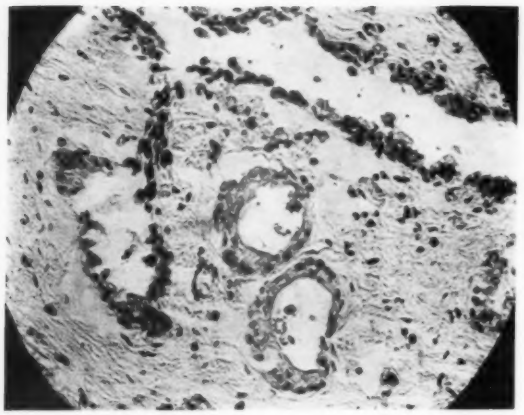

FIG. 6.—Portion of mucosa of ureter, Case III, ×75. The infolding of the mucosa is well shown with healing over of the apposed folds by chronic inflammatory tissue with formation of cysts.

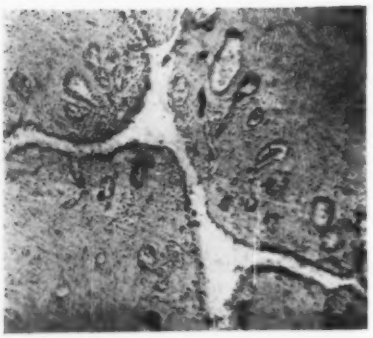

FIG. 5.—Mucosa of ureter from Case III, ×55; showing marked chronic ureteritis with production of cell "nests" and cysts. The epithelial lining has been largely destroyed.

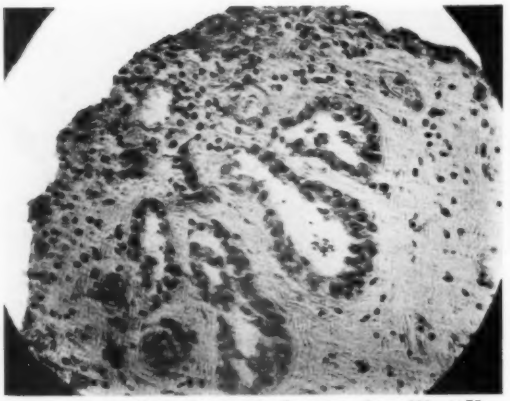

FIG. 7.—A fold of mucosa of ureter, Case III, ×75; showing marked chronic ureteritis and cysts.

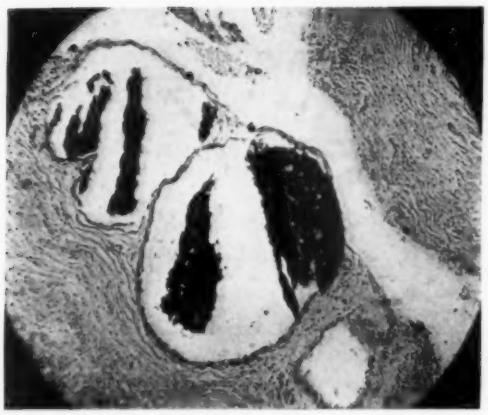

FIG. 8.—The mucosa of ureter, Case III. ×55. The section is through several macroscopic cysts with colloid contents similar to that shown in Fig. 3.

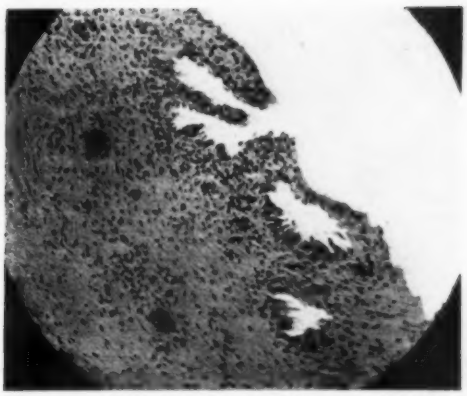

FIG. 10.—A section of the bladder, Case II, ×70. There is chronic cystitis with formation of microscopic cysts from the epithelial "nests" cut off from the lining membrane.

FIG. 9.—Section of ureter, Case II, ×45. The lining epithelium is destroyed, a small cyst is arising from degeneration of the proliferated epithelium of the "nest," a larger cyst is shown, its contents having been lost through faulty technique.

FIG. 11.—The formation of macroscopic cysts in the same bladder as in Fig. 10 is shown. There is very marked inflammatory thickening of the tunica propria with fibrous myositis conspicuous throughout.

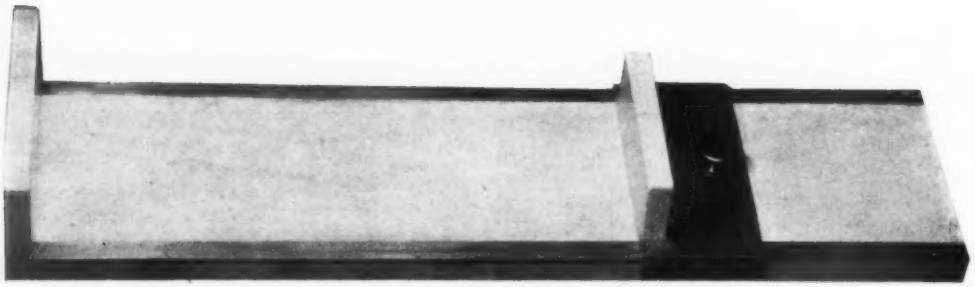

FIG. 1.—Apparatus for measuring the new-born. Constructed from maple wood and painted.

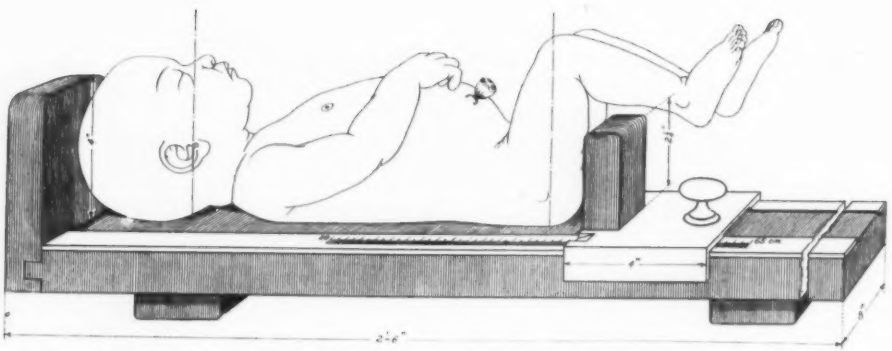

FIG. 2.—Schematic drawing of the measuring apparatus with baby in position for measuring sitting height.

AN APPARATUS FOR MEASURING THE NEW-BORN

By ADOLPH H. SCHULTZ,

Research Associate, Department of Embryology of the Carnegie Institution of Washington

The size, particularly the length, of the new-born baby is of manifold interest. It has been shown to vary to a great extent, to average less in girls than in boys, less in negroes than in whites, and less in twins than in single-born individuals. Furthermore, the number of previous labors of the mother seems to influence the size of the fetus at term, primiparæ in general having smaller children than multiparæ. Variations in the size of the child depend probably also upon the size of the parents and the age of the mother. Numerous other factors, such as nationality, state of nutrition of mother, size and condition of maternal pelvis, etc., have been held responsible for differences in size of new-born infants or have at least been correlated with it. The length is also of great importance in determining the age of a baby, both full term or premature, and in this respect affords a more accurate criterion than weight.

The material upon which those investigations have been based was obtained in most of the cases from the records of obstetrical departments and was usually available in ample amount. However, there is one objection to the use of data relating to size from such records, and that is the method of measuring usually employed. This is only too often absolutely unreliable and very rarely accurate enough to approach scientific requirements. The measuring is frequently not done in a uniform way; suitable instruments are lacking, so that one has to be content with a tape (!), and the babies are not placed so that their positions are analogous in every case. The individual error in those measurements naturally must be very considerable and may amount to more than 10 per cent of the true measurement. Inasmuch as the above-mentioned differences in size under different conditions are mostly rather small and rarely surpass a very small percentage of the averages in length, it is easily seen that conclusions drawn from such crude measurements must be very unsafe.

In contrast to height (or length), the data on weight are very reliable, because here the technique is uniform, the required apparatus fairly accurate, and the chance for error minute. The contrast in accuracy of height and weight accounts partly for the apparently small correlation between the two measurements.

There is no reason why the height could not be obtained almost as accurately as the weight and this with no greater expenditure of time than heretofore. The only two requirements are uniformity of technique (especially of posing the baby) and a suitable apparatus. The former problem is best solved by answering clearly the question of what and how to measure. What one wants to measure is the dimension on the body of a baby, which best represents its size, or rather length. The choice here lies essentially between two measurements—the body length or standing height, and the crown-rump length or sitting height. Most frequently the total length of the body, *i. e.*, from the soles of the feet to the top of the head, is taken. This measurement has two disadvantages: The baby's legs can only with difficulty be stretched straight, and the variable length of the lower extremity is included in the length of the head and trunk. The latter (sitting height) is individually less variable, being composed of fewer elements; it represents, furthermore, the true body length comparable to the body length of other mammals. The sitting height (from buttocks to top of head) should therefore be given first rank. The body height may be taken as a supplementary measurement, of interest mainly for comparison with the sitting height.

The position of the head, *i. e.*, whether it is bent downward or upward, as well as the direction of the thigh, influence the sitting height and should therefore be always the same. This question of how to measure can best be answered by following the custom of physical anthropology and placing the head so that a line through the outer opening of the ear and the lowest point of the orbit (ear-eye line) stands perpendicular to the main axis of the body. For measuring the sitting height the axis of the thigh should also be at right-angles with the axis of the body. In addition, attention has to be paid to the axis of the body or rather the curve of the back, which should be as nearly straight as possible. This is best accomplished by placing the baby on its back on a flat horizontal surface, the latter representing the body axis.

The author has designed a simple but accurate measuring apparatus (Fig. 1.), in which the above directions form guide points. This apparatus is now used with entire satisfaction for routine measuring in the obstetrical department of The Johns Hopkins Hospital. It consists in principle of a horizontal board on which the baby is placed on its back, of one perpendicular board firmly attached to one end of the horizontal or base board, which has to be touched by the top of the head of the baby, and another (sliding) perpendicular board, which can be brought into contact with the buttocks for the measuring of the sitting height or with the soles of the feet for measuring the standing height. The distance between these two perpendicular boards constitutes the required measurement and is read off from a scale attached to the horizontal board. The movable vertical board is mounted on a brass saddle, which slides on the horizontal board and holds the perpendicular board at right-angles to the main axis of the base board. On each of the two lateral edges of the base board a brass strip is inlaid and one of these is ruled in millimeters from 200 to 650, zero being at the end of the base board where it meets the firm perpendicular board. The range of ruling is sufficient for measuring from the sitting height of a fetus at the end of the sixth month to the standing height of an exceptionally large new-born. The brass saddle rests with its lateral

portions on the two brass strips; the center of the saddle is slightly raised to reduce friction to let only metal ride on metal. A small area on the edge of the saddle over the ruled brass strip, on a plane with the movable perpendicular board, is tapered to a knife-like edge to allow accurate reading of the scale. The chief dimensions of this apparatus are given in the schematic drawing of Fig. 2. The same figure shows the position of the baby when posed for measuring the sitting height. The apparatus can easily be made by any instrument maker or carpenter for a cost which should not exceed $15 or $20.[1]

[1] Where it is found impossible to have such an apparatus made, institutions desiring it may secure it in Baltimore by communicating with the author, at the Carnegie Laboratory, Johns Hopkins Medical School.

The apparatus forms certainly an improvement as compared with methods so far in use, and will enable one to measure accurately down to single millimeters. It is very desirable that this or some similar construction should be used by all obstetrical departments, in order to obtain in great numbers reliable data on the length of babies. Statistical treatment of such data in connection with various other factors to be found in histories will no doubt permit the drawing of a whole series of interesting conclusions. These will be the safer and more reliable the more accurately such measurements are made and the more material so treated is available; the latter factor being dependent on the number of institutions adopting this new method.

AN UNUSUAL CASE OF TUBERCULOUS SALPINGITIS

By J. P. Greenberg

(From the Gynecological Clinic of The Johns Hopkins Hospital)

The following case is one of interest because the condition was not recognized before operation, at the time of operation, nor even when the specimen had been removed. The diagnosis made from the history and the physical examination at the time of admission, was "tubo-ovarian abscess." The same opinion was held after examining the patient under ether, just before operation. After opening the abdomen, the diagnosis was changed to "tubal pregnancy, unruptured." The specimen, which was believed to be a tubal pregnancy, was taken to Dr. Streeter of the embryological department of the Carnegie Foundation. The true nature of the mass was not revealed, however, until it was opened.

Report of Case

History.—G. C., Gynl. No. 25479, colored, aged 19, married, was admitted to The Johns Hopkins Hospital on November 17, 1919, complaining of pain, swelling and tenderness in the right lower abdomen. There was nothing noteworthy in her family history. Her general health had been good. She had had pneumonia at 14 and influenza at 18. Marked constipation had been present for many years. There was nothing of importance in the menstrual history save that during the first two days of the flow, there was moderately sharp pain on the right side. The last menstrual period occurred from November 11 to 15, 1919, the preceding one from October 12 to 16, 1919. No leukorrhea had ever been noticed. The patient had been married three years, but had never been pregnant.

Present Illness.—Five years before the patient had had pneumonia and since that time there had been indefinite pains in the right lower quadrant. The pains were usually dull and dragging in character, but there had been acute exacerbations in which they were very sharp. The pains were localized in the right lower quadrant and did not radiate from that location. There had never been any nausea or vomiting. The pains had never been severe enough to cause the patient to go to bed until three weeks before admission. At that time, she was suddenly awakened in the night by very sharp pain in the right lower quadrant. She had had no discomfort at all before going to bed that evening. There was no nausea or vomiting and the patient did not faint. The pain only lasted a short while and the patient fell asleep again. The next day, the pain recurred and she remained in bed. On the following day, she got up and did her housework. The next day, she began to menstruate, this being the proper time for it. With the onset of menstruation, the sharp pain returned and the patient went back to bed. She remained in bed five days, during which time she menstruated and during which time, also, the pain in her right side persisted. After getting out of bed this time, she came to The Johns Hopkins Hospital Dispensary, to find out the cause of her pain.

Physical Examination.—The patient was a well-nourished and well-developed young colored woman in no apparent discomfort. The anterior and posterior cervical glands were enlarged. The lungs were entirely negative to inspection, palpation, percussion and auscultation. At the apex of the heart was heard a soft, blowing, systolic murmur, which was not well transmitted. The breasts did not show anything abnormal. Examination of the abdomen was entirely negative except for definite tenderness all over the lower part, most marked on the right side. On pelvic examination, the body of the uterus was found to be in midposition, of normal size and consistency, but pushed over to the left side. Filling the right half of the pelvis and bulging into the culdesac of Douglas and also into the rectum was a tense, smooth, cystic mass, adherent and tender. No mass was palpable on the left, but there was slight tenderness in the right fornix. The temperature was 98°, the pulse 88, and the respirations 20. The R. B. C. was 4,096,000, the W. B. C. 9920, and the hemoglobin (Sahli) was 75 per cent. The blood-pressure was 118/80, the urine was negative, as was the Wassermann. The impression recorded from the above history and physical examination was, "chronic pelvic inflammatory disease with a tubo-ovarian abscess on the right side."

Under ether, the pelvic examination revealed the following: The body of the uterus was of normal size, in good position, and freely movable. On the right side were two masses which could be made out distinctly. The first mass was globular, with a diameter of about 12 cm., tense, rather cystic and absolutely adherent to the pelvic floor. Lying on top of this mass was a smaller one, oval in shape and measuring about 9 by 5 by 5 cm. The smaller mass was movable within limit and seemed hard. The left side of the pelvis was free. The left ovary was slightly enlarged, but freely movable. The diagnosis made from this examination was "tubo-ovarian abscess, right."

Operation (Dr. R. L. Wharton).—A pelvic puncture was done first, in the belief that the abscess could be drained. The peritoneal cavity was entered, but no fluid was obtained. As it seemed inadvisable to carry the pelvic operation any further, a midline

FIG. 1.

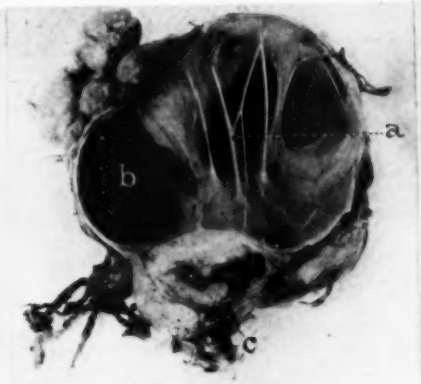

FIG. 2.

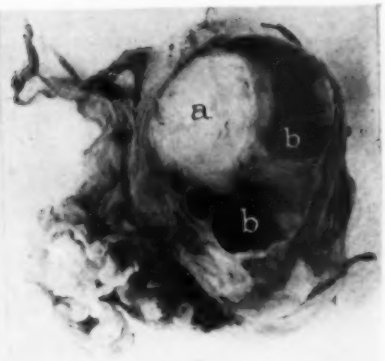

FIG. 3.

FIG. 4.

FIG. 5.

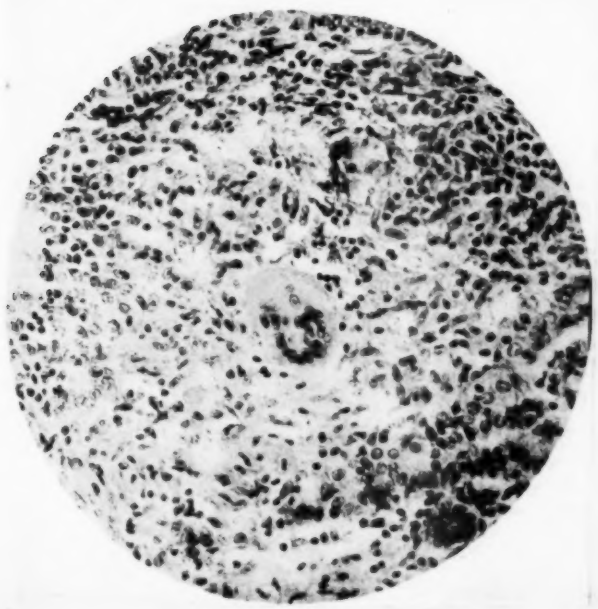

FIG. 6

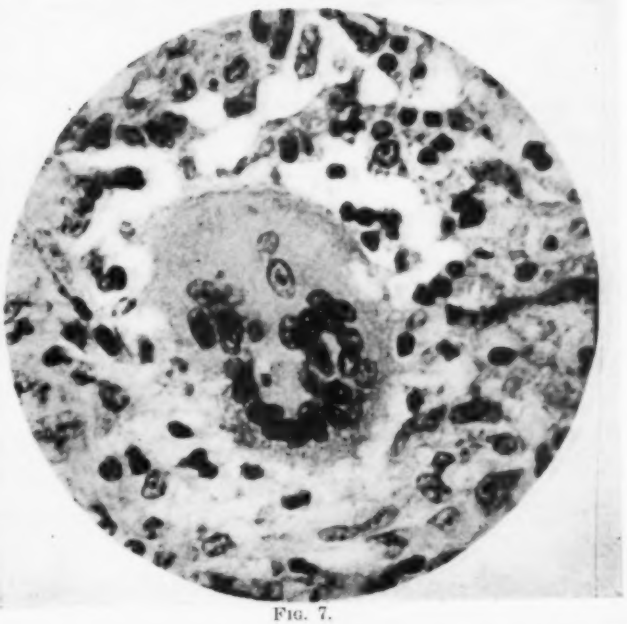

FIG. 7.

abdominal incision was made. Numerous adhesions were found and released without any difficulty or bleeding. Exposure being obtained, the uterus was elevated and found free from adhesions, of normal size and not softened. On the right side two masses were seen. The upper one was bluish in color, cystic, lobulated, and suggested an extra-uterine pregnancy in the outer one-third of the fallopian tube. This appeared to be just on the point of rupturing. By careful dissection, the mass was released, together with the entire length of the fallopian tube, from the mass underneath it. The tube with a wedge of uterine cornu was resected without rupturing (what we thought to be) the gestation sac. The lower, and by far the larger mass, proved to be a corpus luteum cyst. Since the entire cyst could not have been removed without injury to the ureter and rectum, only a portion of it was excised together with the right ovary. On the left side, the fallopian tube was somewhat enlarged and reddened and its fimbriated extremity was closed. As the ovary appeared normal, the tube alone, with a wedge of uterine cornu, was removed. One cigarette pelvic drain was placed through the drainage tract already present, the free end of the gauze lying in the sac of the corpus luteum cyst. The appendix was then removed.

PATHOLOGICAL REPORT

Gross Description.—The specimen consists of the right tube and ovary, the left tube and the appendix. The right tube is of great interest. *In toto*, it presents a typical picture of a tubal pregnancy (Fig. 1). The mass is egg-shaped, measures 8 by 5 by 4.5 cm. and is covered by very fine adhesions. For the most part, the mass is cystic and through the wall one sees a bluish-black discoloration, suggesting that of old blood. The inner portion of the mass consists of the uterine end of the tube and measures 5 cm. in length and 8 mm. in width. It feels very hard. On section, the lumen is found entirely filled with a grayish-white, homogeneous, firm material. The outer, and by far the larger, portion of the mass, consists of the remainder of the tube much dilated. The fimbriated end has been entirely sealed off. On cutting into the mass, one is surprised to find no blood. Instead, there is seen a greenish, gelatinous fluid, filling up a large cavity, crossed by numerous thread-like trabeculæ (Fig. 2). On one wall of this cavity, adjacent to and apparently connected with it, is a discrete, rounded, rather firm mass, greyish-white in color (Fig. 3). This mass extends along almost the entire length of the cavity.

The left tube is coiled upon itself and measures 15 cm. in length. At its widest diameter it is 4 cm. and its entire surface is covered by adhesions. The fimbriated end is closed. At the uterine end, for a distance of about 2 cm., the tube measures 15 mm. in diameter and feels very hard. This same hardness is noted at the distal one-fourth of the tube. On section, these two hard areas disclose the lumen entirely obliterated by greyish-white, opaque, caseous masses, suggestive of tuberculosis. In the area of the tube between these masses, the lumen is markedly increased in size and contains a brownish, gelatinous, friable material, easily separated from the tubal mucosa. The latter is considerably thickened in scattered areas and is very much distorted.

The portion of the ovary present measures 5.5 by 4 by 2 cm. and is covered by adhesions everywhere. To one surface of it is attached a portion of the wall of a corpus luteum cyst. This cyst wall is 3 mm. thick and is easily stripped away from the ovary, save at one small area. On section, the ovary presents numerous small cysts.

The appendix measures 7 by 1 by .75 cm. and feels fairly firm. There are a few adhesions at the base, but none at the tip. Its blood-vessels are injected and the lumen is small owing to the thickness of the appendiceal wall.

Microscopical Description.—Sections through the right tube at about 4 cm. from the uterine end show a marked proliferation of tubal mucosa. The entire lumen is filled with an extraordinary number of villous projections which have fused with one another so that no definite, continuous lumen remains (Fig. 4). The follicular spaces formed by this agglutination contain an abundance of small round cells, among which are found many polymorphonuclears. These spaces are lined with low columnar or cuboidal epithelium, which for the most part is intact and stains well (Fig. 5). Only here and there does one see degeneration or disappearance of epithelial cells. Scattered throughout the stroma are typical tubercles of varying sizes, in which are seen giant cells, epithelioid cells and a marked small-round-cell proliferation (Fig. 6). In a number of places necrotic masses are seen. The stroma shows a marked increase of fibrous tissue and is infiltrated with small round cells. Blood-vessels are few in number. The surrounding wall likewise contains definite tubercles and there is a generalized small-round-cell infiltration. All around the wall dense adhesions are seen. Sections through the caseous mass found in the cystic portion of the right tube (Fig. 3) show a picture similar to that just described, but in a much more exaggerated form. Conglomeration of the tubal folds is much more marked and much of the tissue is necrotic. In numerous places the epithelium has become degenerated and in some areas it has entirely disappeared. These sections show a much greater abundance of connective tissue. Typical tubercles are seen in the wall as well as in the interior of the tube.

The left tube presents a picture somewhat similar to that of the first sections described, but much less pronounced. In the middle portion of the tube, the lumen persists and is increased in size. Numerous tubercles are seen everywhere and there is extensive hemorrhage into the lumen. Around the wall of the tube are dense adhesions. Sections through the proximal and distal ends of the tube reveal similar findings, except that the lumen has been obliterated by the agglutination of folds.

The ovary shows the corpus luteum cyst wall, some hemorrhage into the stroma and adhesions on the surface.

Sections through the appendix show round-cell infiltration; those from the proximal portion showing adhesions in addition.

Diagnosis.—Tuberculous salpingitis, bilateral; chronic appendicitis; corpus luteum cyst of right ovary.

Course in Hospital.—The convalescence was somewhat stormy due to a post-operative pneumonia which developed on the second day after operation. The condition cleared up entirely. The patient was discharged December 16, 1919, and the note made was as follows: *Abdomen:* Incision healed *per primum*. *Vaginal:* Normal except for a hard, round, insensitive mass in right fornix, the corpus luteum cyst, which is absorbing. Temperature during the last few days not above 98°.

I wish to extend my thanks to Dr. Thomas S. Cullen, through whose courtesy I am permitted to report this case and to Mr. Osborne O. Heard for the splendid photomicrographs.

EXPLANATION OF PLATE

FIG. 1.—The right tube as removed at operation. *a* shows the uterine end, *b* the mass mistaken for a tubal pregnancy.

FIG. 2.—Cross-section through the mass, Fig. 1, *b*, showing the trabeculæ, *a*, and the cavity, *b*. At *c*, the lumen of the tube is seen.

FIG. 3.—Cross-section through the mass to show the greyish-white tumor, *a*, and the cavity, *b*.

FIG. 4.—Photomicrograph of section through the right tube, 4 cm. from the uterine end, showing the marked proliferation of tubal mucosa with no definite, continuous lumen.

FIG. 5.—Photomicrograph of section through the caseous mass. This area shows the follicular spaces, *a*, lined with columnar epithelium. Small-round-cell infiltration is seen at *b*.

FIG. 6.—Photomicrograph through the caseous mass. A typical tubercle is seen, showing a giant cell, epithelioid cells and small-round-cell infiltration.

FIG. 7.—Magnification of central portion of Fig. 6.

PROCEEDINGS OF SOCIETIES

THE JOHNS HOPKINS HOSPITAL MEDICAL SOCIETY

FEBRUARY 2, 1920

The Production of an Acute Respiratory Disease in Monkeys by Inoculation with B. Influenzæ. DR. FRANCIS G. BLAKE.

Following the discovery by Pfeiffer of *B. influenzæ*, this organism was generally accepted as the cause of epidemic influenza. Objections to this theory, however, arose when *B. influenzæ* was found to be present in the normal mouth and to be associated with other diseases of the respiratory tract, such as, measles, bronchitis, bronchiectasis, etc. Some observers have gone so far as to say that the influenza bacillus was a saprophyte and had no pathogenicity for man. These objections have little weight since it has been quite thoroughly established that many organisms, whose etiological relationship to respiratory diseases is proved, have been found in normal mouths and have been associated with other pathologic processes. It has furthermore been established that *B. influenzæ* is pathogenic for man, since it is found in cases of meningitis, bacterial endocarditis, pneumonia and other diseases. During the recent pandemic the failure of some bacteriologists to find the influenza bacillus in a certain number of cases led to scepticism as to the etiologic rôle of this bacillus in influenza, and it was relegated to the position of a second invader along with the pneumococcus and other complicating organisms, and the theory was advanced that a filtrable virus was the cause of the disease. Nothing in the way of experimental evidence having been advanced that a filtrable virus is the cause of the disease, we have thought that the influenza bacillus could not lightly be dismissed and relegated to a secondary position. As there was no proof that the influenza bacillus was not the cause of the disease, it seemed desirable to try inoculation experiments on animals to determine what rôle *B. influenzæ* played in the disease, for it has certainly played an important part in the epidemic.

The series of animal experiments was undertaken with Dr. Cecil at the Army Medical School, in Washington. It was clear that previous results obtained by different observers were often very conflicting. It was also evident that the majority of previous animal inoculation experiments had little direct bearing on the possible relation which the influenza bacillus might have to influenza, since most of the inoculations had been intraperitoneal, subcutaneous or intravenous, and it was not to be expected that the disease which is a respiratory infection could be produced in animals by other paths than the natural path of entry in man. It seemed, therefore, that if we were to obtain information as to the rôle of *B. influenzæ* it would be necessary to inoculate the mucous membrane of the respiratory tract. It also seemed to us that probably the lack in results from animal inoculation experiments might be largely due to our meager knowledge of the influenza bacillus, and also to the failure to take into consideration that such pathogenicity as the bacillus possesses is easily lost outside of the body. Because the means that we have for distinguishing between possible pathogenic and saprophytic strains are entirely inadequate, it was decided in our experiments to use one strain, one that had been given us by Dr. Rivers and that had been isolated in pure culture from a case of empyema following a case of influenza. It has been discovered that the monkey was the best subject, and these animals were used for the experiments. The animals were fresh stock, which had recently arrived. They were thoroughly healthy, normal animals, and we used no means to injure the respiratory tract in any way in advance, before inoculation. As is well recognized, the use of monkeys in the production of infectious diseases requires caution in the interpretation of temperature and leucocyte changes as indicative of infection in the absence of other supporting evidence. This is particularly so with *B. influenzæ*, because the toxic effect of influenza bacillus cultures and culture filtrates are such that care has to be taken that the results obtained are from actual infection and not from the temporary intoxication. In our experiments temperatures and leukocyte counts were taken daily, clinical symptoms recorded, cultures from the nose and throat and blood made. Since none of our cases were fatal, most of the animals were killed either in the acute stages of the disease, or while convalescing, and autopsies with bacteriological studies were made. The bacillus used was isolated from a chronic empyema fluid, following a case of influenza. It was demonstrated to be a Gram-negative, non-motile, hemoglobinophilic bacillus. When it was received it had been in culture for about 6 weeks, on artificial media and was avirulent for white mice. In a preliminary test a monkey showed no evidence of infection and it was evident that the organism would have to be raised considerably in virulence before successful results could be obtained. This was done by animal passage, through a series of 11 white mice and then through 13 monkeys by intraperitoneal inoculations. It was found at first that *B. influenzæ* began to disappear from the peritoneal cavity of the inoculated mice by the end of 8 hours and was gone entirely by the end of 24 hours. Consequently the mice were killed after from 6 to 8 hours. After the organism had been passed through 11 mice, monkeys were substituted. The monkeys showed great variation in reaction to intraperitoneal inoculation. The symptoms were those of peritonitis and severe intoxication with leucopenia. At the completion of the series of intraperitoneal inoculations the organism was found to be fairly virulent, 0.01 c. c. of a blood-broth culture killing mice within 48 hours. This virulence was easily lost on culture outside of the body, and it was therefore necessary to use cultures but recently removed from the previous animal. For inoculation of the respiratory tract the material consisted of first or second subcultures taken from the peritoneum of a monkey dying from influenza peritonitis or from the respiratory tract of those having influenza pneumonia, or of the peritoneal exudate

from those dying from influenza peritonitis. The culture media were chocolate-agar plates or blood-broth. In using peritoneal exudate the purity was controlled by direct smears and culture. It is impossible to state whether one method gave better results than another. Two modes of inoculation were employed. In one inoculation was made in the upper respiratory tract to determine whether *B. influenzæ* could initiate an infection of the upper respiratory tract, and if so, what the nature of the infection might be. In the other inoculations were made directly into the trachea. The purpose of this was to study the pathologic characteristics of the pneumonia if such were produced. It seems wise to present these two series of experiments since they are of quite different significance.

We will take up first those inoculated in the upper respiratory tract. Twelve monkeys were inoculated in the nose and mouth. The amount of culture or peritoneal exudate varied. Four monkeys were inoculated simply by swabbing the mucous membranes with an applicator previously dipped in the culture, 2 monkeys had 0.25 c. c. in each nostril and the mouth, one had 0.5 c. c. in each nostril and the mouth, 2 had 0.8 c. c. in each nostril and the mouth, and 3 received 1 c. c. in each nostril and the mouth. In each instance there developed an acute respiratory infection of from 3 to 6 days' duration. The severity of the diseases bore no apparent relation to the amount of material used in inoculation. The onset of symptoms occurred quite suddenly from 3 to 6 hours after inoculation. The first symptom in all cases was a varying degree of prostration, often extreme, the monkeys lying prostrate on the floor of the cage, and sometimes pressing the hands tightly over the top of the head. This symptom was quite different from the symptoms of the onset of pneumococcus pneumonia in monkeys. In that disease there was never prostration at the onset, the disease being detected only by temperature rise, leucocytosis and accelerated respirations. In the influenza cases, simultaneously with the appearance of prostration, there was an abrupt temperature rise in some cases, but in others there was practically no fever. The symptoms of the respiratory tract infection soon followed; frequent sneezing, rapid blinking of the eyes, suggesting possible photophobia, and rubbing of the nose occurred. The subsequent course of the disease was in general that of a self-limited, respiratory disease, the acute stage of which lasted from 3 to 6 days. Three monkeys were allowed to survive and in these a considerable degree of weakness which lasted for some time was observed. By the end of from 24 to 48 hours the infection had spread from the upper respiratory tract to the lower respiratory tract, which was evidenced by a cough. This was again quite different from the cough of pneumococcus pneumonia in monkeys. In the lobar pneumonia cases the cough was slight and developed late in the course of the disease. In the influenza cases the cough was severe and very frequent. About this time a variable amount of mucoid exudate began to be excreted from the nose of the monkeys. In some cases this became muco-purulent later on, but in some it remained mucoid and scanty. Smears of this made 24 hours after inoculation not infrequently failed to show the influenza bacillus. The temperature reaction varied greatly and showed no constant curve. One feature of this temperature curve which was fairly constant was a fall in the temperature on the third day with a subsequent rise. Leucocyte counts showed either a definite leucopenia or no significant total variations from the normal. The differential count showed that there was an initial increase in polymorphonuclears of short duration which rapidly fell to a normal or subnormal. In 3 cases only did leucocytosis develop, and that on the third or fourth day in association with an acute purulent sinusitis. No great stress can be laid on the variation in the leucocyte count, but the absence of leucocytosis which has invariably occurred following intratracheal inoculations with Pneumococcus or Streptococcus hemolyticus would seem to be of some significance. The complications that occurred in this series are of considerable interest. An acute purulent sinusitis developed in 5 cases, this condition being quite analogous to the sinusitis which complicates influenza in man. Cultures from the antra showed abundant influenza bacilli in 3 cases, a moderate number in 1 case, and none was recovered in 1 case. Two monkeys developed a recognizable pneumonia in 3 or 4 days. The onset of the pneumonia was insidious, and the disease was suspected only by a rise in temperature and respiration rate. At autopsy *B. influenzæ* was discovered in pure culture in the lungs. A third case of pneumonia found on pathological examination was so slight that it was not recognized during life.

The second group, in which the inoculations were made into the trachea consisted of 10 monkeys. Of these 7 got pneumonia, 2 tracheobronchitis without actual pneumonia and another resisted infection altogether. In 2 cases infection passed from the lower respiratory tract into the upper tract with the usual developments of sneezing, rhinitis, etc. None of these cases was fatal. One animal developed septicæmia and pericarditis. Cultures from the lungs at autopsy showed the presence of influenza bacilli in pure culture.

The pathologic lesions cannot be shown by lantern slides. At autopsy the mucous membranes of the nasal cavity were swollen, injected and bathed in mucoid or mucopurulent exudate. The antra presented a similar appearance and contained a mucopurulent exudate. Histological sections show edema and congestion of the mucosa, swelling and desquamation of the epithelium and infiltration with leucocytes and lymphocytes. The mucous membranes of the trachea and bronchi showed a similar inflammatory process. In the monkeys with pneumonia there was an intense bronchiolitis. The pneumonia was characterized by its widespread distribution, intense bronchitis and bronchiolitis, areas of peribronchial consolidation, wide-spread hemorrhage, and a marked patchy vesicular emphysema. The pleuræ were only slightly or not at all involved. In one case very marked dilatation of the bronchi approaching bronchiectasis occurred. The influenza bacillus was recovered from the nasal mucous membranes, the antra, the trachea and the bronchi, either in pure culture or in association with other

bacteria that are normal inhabitants of the upper respiratory tract of monkeys. From the lungs it was recovered in pure culture.

In summarizing it is desired to lay particular stress upon the results obtained in the series of 12 monkeys inoculated in the upper respiratory tract. This series of experiments has shown that *B. influenzæ* can initiate in normal animals an acute infection of the mucous membranes of the upper respiratory tract which may spread by continuity to the lower respiratory tract; that the disease so produced is characterized by sudden onset with prostration, and is accompanied by either a leucopenia, or an absence of leucocytosis, and that it runs a self-limited course of brief duration. It may be complicated by acute purulent sinusitis and a type of bronchopneumonia which has been ascribed to influenza bacillus infection of the lungs of man. Control experiments with highly virulent pneumococci and hemolytic streptococci have shown that these organisms do not possess the property of initiating an infection of the normal mucous membranes of the upper respiratory tract and that they must be introduced into the lower respiratory tract before they will initiate infection. This group of experiments is believed to be evidence in favor of the possible primary etiologic rôle of *B. influenzæ* in influenza.

The second group of experiments is of little significance in this respect. They do serve to show, however, that the type of pneumonia in man that has been ascribed to infection with *B. influenzæ* can be satisfactorily reproduced in monkeys with the organism and therefore complete Koch's postulates with respect to bacillus influenza pneumonia.

DISCUSSION

Dr. A. L. Bloomfield.—It is very interesting to hear of this disease which has been produced in monkeys by the influenza bacillus. As Dr. Blake describes it, it seems to resemble influenza, but I should not be at all prepared to accept it as identical with the epidemic disease seen in man. We are still in doubt as to the relation that the influenza bacillus has to the epidemic disease.

When the epidemic first appeared in 1918, the main evidence in favor of the influenza bacillus was its presence in almost every case. Since the epidemic of last winter, however, many observers have had ample opportunity to see that the influenza bacillus can be recovered from the normal mouths of healthy individuals in many cases if proper media are employed. In the second place, as Dr. Rivers has shown by his work, we are dealing with a great variety of organisms, a large group, so that until this group is separated out into its various component strains, it seems barren to discuss the relation of the influenza bacillus to the disease.

I do not believe we can altogether neglect the negative experiments which are carried out by Leake, Rosenau and others, who inoculated healthy people with the secretions from actual cases as well as with freshly isolated strains of influenza bacillus. In none of these individuals was epidemic influenza produced.

Dr. W. G. MacCallum.—Dr. Blake's description of the pathological lesions produced by the introduction of the influenza bacillus are interesting because the lesions are so familiar. They are exactly those that we found in the pneumonias following influenza which were caused by the influenza bacillus. But he concluded by saying that these are the lesions found complicating pneumonia following epidemic influenza, and I do not agree with that, because we found very different forms of pneumonia after epidemic influenza according to the bacteria concerned. While this type resulted when the influenza bacillus was present alone, a very different pneumonia was found when it was due to the pneumococcus, and this in turn was quite unlike that produced by a hemolytic streptococcus.

We have learned that the type of pneumonia depends very strictly upon the nature of the predominant secondary or bacterial invader, and upon the state of resistance of the individual. In the cases in which the influenza bacillus is the secondary invader, there is a considerable induration about the bronchioles, involving the neighboring alveoli. It is an interstitial bronchopneumonia only slightly different from that produced after measles by the hemolytic streptococcus. But in a few cases in which resistance seems to have failed, the peribronchial infiltration is slight and is masked by a great outpouring of blood.

The extraordinary pathogenicity of the influenza bacillus used by Dr. Blake is very striking, but I do not see that it throws any light upon the nature of epidemic influenza to demonstrate that the influenza bacillus like the streptococcus is a serious pathogenic agent. The experiments show that a febrile reaction with prostration and leucopenia can be produced in animals, but those are also effects of other bacteria, and the one character of epidemic influenza which is easily recognizable, its explosive spread through the population, is of course not evident.

Dr. T. M. Rivers.—It is needless to say that I am very much interested in Dr. Blake's work. He has been kind enough to inform me from time to time of his progress. I think he has demonstrated experimentally what was known in 1897, for at that time Meunier reported a series of cases of pneumonia from which pure cultures of *B. influenzæ* were recovered from the blood and lungs, both before and after death (lung punctures were employed to obtain cultures before death). I should like to think that the influenza bacillus caused the epidemic, because that is the only tangible thing we have at present. If influenza is not caused by the bacillus, we must put this disease on the shelf with measles, scarlet fever, smallpox, and such diseases, and that shelf is already full enough.

In the first epidemic, 1918, *B. influenzæ*, when looked for properly was found in 100 per cent of the cases, and in this epidemic, 1920, it has been found in 120 per cent, that is, often *B. influenzæ* of more than one kind has been recovered from the same mouth. The group of Gram-negative hemoglobinophilic bacilli is certainly a large one which can be subdivided by cultural characteristics. Some are hemolytic,

and if "chocolate agar" or Avery's medium be used exclusively, the hemolytic ones will be carried side by side with the non-hemolytic ones and the bacteriologist will be none the wiser, calling them all influenza bacilli.

It is very likely that these bacilli will be grouped culturally and immunologically. So far only one constant group has been made out and that is the meningitic one. Seven strains have proven to be alike culturally and by agglutination tests. From the throats of normal people and influenza patients an organism has been obtained a few times which was similar to the ones in the meningitic group. The bacillus with which Dr. Blake was working probably falls in the meningitic group. It was obtained in pure culture from an empyema in a child and agglutinated 1-1280 with a serum made by immunizing a rabbit against a meningitis strain, the titer for the homologous strain being 1-2000.

The presence of the influenza bacilli in 100 per cent of the cases of influenza does not prove that it is the cause of the disease any more than the presence of *B. coli* in 100 per cent of the stools of typhoid patients proves that it is the cause of typhoid fever and vice versa. It will be necessary to group these organisms and then definitely link a certain strain or strains with the disease influenza before their etiological claims can be established. At present the proof still seems to be lacking.

Someone might be cruel enough to ask Dr. Blake how he knew the bacillus recovered after passage through mice and monkeys was the same as the one sent him. Supposedly it was, I hope Dr. Blake is right.

DR. W. H. WELCH.—Dr. Blake, it seems to me, has forestalled every criticism which may be raised. Whatever may be the relation of the organism to the epidemic disease, he has certainly made a very interesting and valuable contribution to the study of the pathogenic character of the influenza bacillus. The prevailing view has been that the influenza bacillus is a secondary invader like the pneumococcus and other organisms. When we saw the first autopsies in 1918, I was impressed by a certain characteristic of the lesions; these wet, hæmorhagic, soggy lungs and the bronchopneumonic types. Dr. MacCallum has shown me some with dilatation of the atria and marked hyalinization of the epithelial lining. This showed up very clearly with a good acid strain. It has been found that this occurs also in the pneumonia produced by gas poisoning, and also in the experimental pneumonia produced by various chemicals. There was a coagulative necrosis in which the nuclei of the cells lining the dilated atria of the lungs had disappeared. I do not claim that they are present in all cases, but I should like to see them in some case which is under suspicion or which is known to have been caused by the influenza bacillus. I only know of one definite characteristic of this disease, and that is that it spreads like wildfire. It may be that we have scattered, abortive cases, which light up occasionally into epidemics, but we have no means of recognizing these scattered cases if they do exist. It is the rapid spread over large areas of country that makes it so extremely discouraging to work with experimentally. We have no test that we can apply and say "here is influenza." If the influenza bacillus is the cause of the disease it must be some strain with some cultural characteristic which we are at present unable to identify. I am distressed to learn that the influenza bacillus that Dr. Blake is dealing with falls into the group of meningitis bacilli. I should have said that it would fall in with any other group or strain than the meningitis strain. There are reasons why I think one is justified in taking a position that some strain of the influenza bacillus may be the cause of the epidemic influenza. I think that this epidemic is likely to pass away and we are no more familiar with the control of the disease than we were in the epidemic of 1899. It is humiliating, but true.

DR. F. G. BLAKE.—I wish to agree with many of the criticisms that have been made. I have no desire to advance these experiments as proof that the influenza bacillus is the cause of epidemic influenza but merely as evidence in favor of it. I am quite certain that they do not prove it. I think Dr. Welch is right when he says that the only way to prove it is to produce an epidemic in a large group of healthy men. I think all arguments concerning the pathologic characteristics of the lesions in the pneumonia cases is entirely beside the point in considering the question of primary etiology. The important point is that the influenza bacillus can initiate an infection of the upper respiratory tract producing a disease essentially like influenza in man, whereas other organisms commonly found in influenzal pneumonia cannot do so, in monkeys at least. This does not prove that it is the cause of influenza, but appears to us very suggestive evidence. It is an experimental demonstration that the syndrome of influenza in man can be produced in monkeys by inoculation with *B. influenzæ*.

With regard to the hyalinizing membranes of the atria, we looked for it in our monkeys, but did not find it. This result we attribute to the fact that the cases which exhibited the lesion were very severe and rapidly fatal, extremely virulent. In our monkeys we were unable to produce a form virulent enough to produce the hyalinizing membrane.

FEBRUARY 16, 1920

1. Presentation of Two Cases of Epilepsy Apparently Cured by a New Form of Operative Treatment. DR. WALTER E. DANDY.

These cases are presented to the Medical Society in order to demonstrate the results of a new treatment for epilepsy. From observations made at numerous operations upon the brains of epileptics I have come to the conclusion that epilepsy is due to a definite lesion of the brain, and am encouraged to a hopeful outlook for its treatment.

The first patient is a miner, thirty-four years of age. Until the onset of his present illness he has been perfectly well. Briefly, his illness may be summarized as follows: Six months ago, without any warning, he was suddenly seized with a convulsion, which began in the right half of his tongue, the right side of his face; and passing down the right arm and leg, soon involved the entire body. He was unconscious for probably

a few minutes; and after recovering from the attack he had a marked defect of speech and a weakness of the right arm and leg. These sequelæ soon cleared completely, but a series of *petit mal* attacks supervened and have persisted with equal severity but increasing frequency until the time of admission. After he came under our care the attacks were remarkably constant in type and had a most striking periodicity. Every three minutes day and night a characteristic jerking would begin in the right side of his tongue and face and persist in this sharp localization for fifty to sixty seconds. During each twenty-four hours, therefore, about 250 of these attacks developed, there being no mitigation during sleep. A little dysarthria was noted, but quickly disappeared. There was no progression of the attack beyond these precise limits and no loss of consciousness. The third and fourth year students have seen these attacks in ward rounds and clinics, and will quickly note the change in his condition. The diagnosis of Jacksonian epilepsy was apparent.

An exploration of the left cerebral hemisphere disclosed a sharply defined lesion in the pre-Rolandic area, in the region of the second and third frontal convolutions, Broca's area, the face and tongue center. In these regions the pia-arachnoid membrane was greatly thickened, giving a markedly opaque covering over this part of the brain. Under this thickened membrane there was a considerable accumulation of fluid which had a distinctly yellow tint. When the membrane was pricked and the fluid released it was quite evident that the surface of the underlying brain had become softened, and in one area, about 1 x 1 cm. it was very definitely of a brownish color. Below this superficial coat of softened cortex, the brain showed no discernible change. The entire affected zone of brain and the superimposed membranes and the subarachnoid cyst covered an area probably 6 x 6 cm. Elsewhere the brain and its coverings were apparently normal. The sharp delineation of the affected area and the contrast to the adjacent normal brain were easily apparent, even to an inexperienced eye. There could be no doubt that such a sharp lesion so precisely located must have an etiological bearing upon the production of these focal attacks.

A lesion of this character, I believe, is to be found in most cases of epilepsy. It is frequently localized, although often in severe cases the entire surface of the brain may be involved. How it brings about the attacks is largely conjectural. It seems probable that direct implication of the pyramidal tract by this lesion is responsible for the motor manifestations of the epileptic seizures. The cerebrospinal fluid accumulation forming a subarachnoid cyst may be the inciting agent and account for the periodicity of the attacks; that is, the circulation of fluid by filling and discharging seems to account for the onset of the attacks and the latent period, respectively. Working on this assumption, the rational treatment would appear to be the permanent obliteration of the cyst so that it could not refill with cerebrospinal fluid and "set-off" the pyramidal tract. From experiments on animals it was found that iodine efficiently obliterated the subarachnoid space. In this patient the cystic areas were opened with a needle, the fluid released, and the spaces injected with iodine. The irritant action caused adhesions in the course of a few days, and consequently a permanent closure of the cyst. Since the lesion in this patient involved Broca's area, we could not avoid producing temporarily a complete motor aphasia (direct action of the iodine). This has since cleared up completely. The day following the operation the patient had a general convulsion and one or two focal seizures, but since then (it is now twenty-five days since the operation) there has been no semblance of an attack.

Two years ago I used this operation for the first time on a boy eight years of age with focal epilepsy. He had had four or five attacks daily for several years prior to the operation. A few attacks persisted for several days after the operation, but at the end of two weeks they had entirely ceased and have not returned to date (two years). The same pathologic lesion of the brain was found and the same iodinization performed. I know of no other cases of epilepsy with a similar history which have gone this length of time without an attack after any medicinal or operative treatment. However, in view of a certain capricious nature of the disease, it is too much to presume that this treatment will prove successful until many more cases have been treated and a longer time has elapsed; the results in these cases, however, are too striking to be explained as coincidental.

2. An Unusual Instance of Ventricular Escape. DR. E. P. CARTER.

3. The Relationship Between Alkali Retention and Alkali Reserve in Normal and Pathological Individuals. DR. W. W. PALMER.

It is now well known that the chief mechanism in the blood for maintaining a constant reaction is the balanced solution of the carbonates. The bicarbonates are in the blood in about a 0.03 molecular solution, or when estimated as free CO_2, about 55 to 70 volumes per cent. Normally, this bicarbonate level in the blood is maintained with extraordinary constancy. This is effected by the renal and lung mechanisms. When the bicarbonate level in the blood diminishes by reason of a pathological process going on in the body or by reason of the mechanism which regulates this level breaking down, there is a reduction of the level of sodium bicarbonate in the blood. This condition, you remember, has been called *acidosis*, and is generally so called now, or, by the more recently introduced term, *reduced alkaline reserve*. The use of sodium bicarbonate to correct this state of acidosis was first introduced by Stadleman in 1883. He, as you will remember, was the first investigator to discover an abnormal acid in diabetes urine. Ever since he introduced the use of bicarbonate, it has been used a great deal, not only for acidosis, but in a great variety of instances in clinical medicine. It has been also observed for many years that the administration of sodium bicarbonate will produce after a time a strongly alkaline urine. The amount necessary to accomplish this has been noted to be quite variable. No particular attention had been paid to this fact until in 1912

Sellards, working in this clinic, studied the effect of sodium bicarbonate when administered in nephritis, particularly chronic nephritis, and found that it could be used more or less as a crude measure for the degree of acidosis. At the time the criterion for the effect was the reaction of the urine to litmus. Independently, and without knowledge of Sellards' studies, working with Henderson, I observed the same fact and that it could be used as a measure for acidosis in a very crude manner. The criterion that I used was the variation of the hydrogen-ion concentration in the urine. It was found that in any individual, where the blood bicarbonate was normal, the ingestion of a small amount would markedly influence the hydrogen-ion concentration in the urine within an hour, while in pathological cases, where there was known to be an acidosis, a large amount was necessary before any influence on the urine was noted. This was a crude method, but we were looking for some simple test which could be used clinically, and we also recognized the fact that renal function may play a very important rôle in this phenomenon, and that, instead of measuring acidosis, the kidney might throw us off the track by not excreting the alkali until we had given more than was necessary. At that time there was no good method existing for measuring the blood bicarbonate directly. In 1915 an apparatus was devised by Van Slyke by which blood bicarbonate could be measured in the blood. It was noted in 1915 that the kidneys acted nearly normally in response to bicarbonate in cases of severe nephritis, where large amounts of an alkali were necessary before any effect could be noted in the urine. After this the alkali was stopped, the urine allowed to come back to its former acidity, and then one dose of 5 gms. given. Then the kidneys reacted as in a normal case. We thought this a good criterion and that a good check on this method would be to study the relation of the alkali retention to the alkaline reserve. This was done. The method of experimentation was very simple indeed. Blood was withdrawn about two hours after a meal, the bladder emptied, the pH determined, sodium bicarbonate administered in about 2 gm. doses at half-hourly intervals until the effect of the sodium bicarbonate was manifest. It was our purpose to reduce the action of the urine to the reaction of the blood. It was found that when the reaction of the urine had been depressed to the reaction of the blood, then the blood bicarbonate level varied within the upper limits of the normal, that is, about 70 ± 5 volumes per cent. In pathological cases we found quite a different state of affairs. When the urine was depressed to the reaction of the blood, the blood bicarbonate was much above the normal limits. In one case 104 volumes per cent was found. We were most fortunate in not encountering any unpleasant effects in our work, for since then we have heard of several cases in which tetany was induced by the use of large amounts of sodium bicarbonate. We found that the only desirable way to control it was by the CO_2 determinations in the blood. At the Presbyterian Hospital, with the assistance of Dr. Salvesen, this work was carried still further. The object was to find what the blood bicarbonate level would be if taken at the time when the urine showed its first effect. We have studied 24 pathological cases, taken from a variety of conditions. In the 24 cases we found no case in which the bicarbonate was at a dangerous level, and practically all were within the upper limits of normal. This seemed to me most important in a good many ways. For instance, it is not always possible to control the administration of sodium bicarbonate in cases of known acidosis by methods that we are able to use in a well-organized hospital, where we are able to determine frequently the blood bicarbonate, but in general practice it does give a simple method of controlling the administration of alkali and makes such administration perfectly safe. There is the possibility of producing tetany by the use of too much bicarbonate, and it is not desirable to give any more than is necessary by mouth because of the gastro-intestinal symptoms that may arise. If enough alkali be given to depress the urine below the reaction of the normal blood, albuminuria may be produced, which, of course, can be cleared up rather quickly if the sodium bicarbonate be discontinued. It is not my purpose to take up the use of bicarbonate, but to point out the fact that it may be used safely in a very simple way.

DISCUSSION

Dr. John T. King, Jr.—I should like to ask just one question. I think that Dr. Sellards had the idea when he administered bicarbonate by mouth, that there were a certain number of individuals who had a definite diminution of the alkalis in their bodies as a whole with little change in the blood. In these it took a considerable amount of sodium bicarbonate by mouth to produce any effect on the urine, while the blood alkalinity showed relatively little change. In these cases he thought that the blood tended to reserve its alkali reserve at the expense of the tissues. What light does your method show on this?

Dr. Palmer.—I had not mentioned this because of the introduction of too much mathematics into the paper. We found that if you calculate the body fluid on the basis of about 70 per cent water, you can calculate with a great degree of accuracy the effect the bicarbonate is going to have on the blood CO_2. We found no difference in the blood and the body fluid and the sodium bicarbonate was distributed with great rapidity and ease, so that I think that is not so.

Dr. Clyde Guthrie.—In addition to the effect of sodium bicarbonate already mentioned, I was under the impression that this substance might be retained in the body in various localities. A case in point is the reason for this question. A patient with a nephrosis had an intensive course of alkaline therapy, and I am uncertain whether at the time he had developed œdema. Certainly following this therapy he developed it and likewise an ascites. Fluid was taken from his abdomen and found to be very strongly alkaline and the addition of dilute acetic acid made it effervesce in an extraordinary manner. It was my impression that the sodium bicarbonate was in this

instance retained in the body at a point perhaps outside of the circulation.

DR. PALMER.—I was responsible for this therapy and I think I should explain my part of the responsibility. He had been on the ward for some months, and was becoming impatient because he was not being treated. I have seen cases of this kind with œdema, where acid urine was present. After changing the reactine of the urine, bringing it to neutral, diuresis occurred. This was tried on this man and he gained remarkable amounts of fluid. I don't believe it did the man very much harm.

4. Contributions to Psychopharmacology. DR. D. I. MACHT.

To be published later.

BIOGRAPHY OF SIR WILLIAM OSLER

Lady Osler has requested me to prepare a biography of her husband, and I will be most grateful to anyone who chances to see this note, for any letters or personal reminiscences, or for information concerning others who may possibly supply letters.

Copies of all letters, no matter how brief, are requested, and if dates are omitted it is hoped that they may be supplied if possible.

If the originals are forwarded for copy they will be promptly returned.

HARVEY CUSHING, M. D.,
Peter Bent Brigham Hospital,
Boston, Mass.

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